- x
:
FIFRA SCIENTIFIC ADVISORY :
:
PANEL (SAP) OPEN MEETING :
:
- x

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

February 5, 2002

[8:30 a.m.]

SHERATON CRYSTAL CITY HOTEL
1800 Jefferson Davis Highway
Arlington, Virginia 22202

PARTICIPANTS

FIFRA SAP Session Chair

Ronald J. Kendall, Ph.D.

Designated Federal Official

Mr. Paul Lewis

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Christopher J. Portier, Ph.D.
Stephen M. Roberts, Ph.D.
Mary Anna Thrall, D.V.M

FQPA Science Review Board Members

John Adgate, Ph.D.
William Brimijoin, Ph.D.
Richard Bull, Ph.D.
Rory Conolly, Sc.D.
Patrick Durkin, Ph.D.
Natalie Freeman, Ph.D.
Jean Harry, Ph.D.

Steven Heeringa, Ph.D.

Ernest McConnell, D.V.M.

Peter MacDonald, D. Phil.

Nu-May Ruby Reed, Ph.D.

Lorenz Rhomberg, Ph.D.

Lauren Zeise, Ph.D.

DR. KENDALL: Good morning. I'd like to welcome everyone to the February 5, 2002, meeting of the Scientific Advisory Panel to discuss the Cumulative Risk Assessment for Organophosphate Pesticides. My name is Ron Kendall. I'll be chairing the next several days.

And at this point, we would like to introduce all the panel members. We had a few minutes to meet this morning to get organized, to get going. This is going to be a very challenging meeting. The amount of material received to date had been extraordinary. And we appreciate the effort of EPA in moving this process forward and giving us an opportunity to continue to review and contribute where possible.

I'd like to go ahead and introduce the panel members as we do as standard procedure. Dr. Bull, we start with you, and we'll move around the table.

DR. BULL: How much history do you need?

DR. KENDALL: Name, rank, serial number.

DR. BULL: I'm Richard Bull. Washington State University. My area is toxicology.

DR. KENDALL: Please use the microphones. And Dr. Bull, really, the name of area of expertise and affiliation, please.

DR. BULL: Richard Bull, Washington State University, toxicology.

DR. DURKIN: Pat Durkin, Syracuse Environmental Research Associates. I do pesticide risk assessments primarily for the USDA.

DR. HARRY: Jean Harry, National Institute of Environmental Health Sciences. Research area is in neurotoxicology.

DR. RHOMBERG: Lorenz Rhomberg. Gradient Corporation. I'm also an adjunct professor at The Harvard School of Public Health. And I'm interested in quantitative risk assessment methodology.

DR. CONOLLY: Rory Conolly, CIIT Centers for Health Research in Research Triangle Park, North Carolina. I'm interested in the mechanisms of toxicity that underlie the shape of the dose response curve and the use of biologically based models in risk assessment.

DR. MCCONNELL: Gene McConnell, Toxpath, Raleigh, North Carolina. My area of interest is experimental comparative pathology and toxicology.

DR. BRIMIJOIN: I'm Steve Brimijoin, Department of Pharmacology, Mayo Clinic. I do research on pharmacology and toxicology of cholinesterases.

DR. ROBERTS: Steve Roberts. I'm a toxicologist at the

University of Florida. I'm a professor with a joint appointment in the College of Medicine and the College of Veterinary Medicine. My interests are in mechanisms of toxicity and, also, in risk assessment.

DR. PORTIER: Chris Portier from the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. I direct the environmental toxicology program and sort of direct the national toxicology program. My area of expertise is biostatistics and risk assessment.

DR. ADGATE: John Adgate, University of Minnesota School of Public Health. My expertise is in exposure assessment and risk assessment methods.

DR. FREEMAN: Natalie Freeman, Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. My areas of expertise are exposure assessment in the residence and children's exposure.

DR. REED: Nu-May Ruby Reed from California Environmental Protection Agency, Department of Pesticide Regulation. I am a toxicologist doing pesticide risk assessment.

DR. MACDONALD: Peter MacDonald from Mathematics and Statistics at McMaster University in Canada. I have a general expertise in applied statistics and model fitting.

DR. HEERINGA: Steve Heeringa, the University of Michigan Institute for Social Research. I'm a biostatistican. I direct research operations for the institute there at the University of Michigan.

DR. KENDALL: Thank you. My name is Ron Kendall. Again, I'll be chairing the session today. I serve as chair of the SAP. And I have enjoyed working with this very fine group at the SAP. I'm from Texas Tech University. I'm professor and chairman of the university's Department of Environmental Toxicology. I also serve as director of the university's Institute of Environmental and Human Health.

I wanted to just say a special word of thanks for the staff's efforts to make sure this panel, this very fine panel, gets here okay as coordinated. I thank Larry Dorsey, Shirley Percival, and the rest of the group, Larry's very fine staff, who always do a great job. And it's going to be my pleasure to work with Paul Lewis. Paul and I served for years together. And I turn it over to you, Paul, for any administrative procedures. Thank you.

MR. LEWIS: I think you, Dr. Kendall. Again, it's a pleasure to work with you and for the members of the panel for another meeting with the Scientific Advisory Panel. I would like to welcome the panel members and the public to this important meeting of the FIFRA Scientific Advisory Panel addressing methods used to conduct a

preliminary cumulative assessment for organophosphate pesticides.

And I, also, want to thank the panel for agreeing to serve at this meeting and for their time preparing for this meeting and the upcoming deliberations that will happen over the next four days. Also, to my colleagues on the EPA staff and my colleagues with the Scientific Advisory Panel for their efforts in preparing for this meeting today and for the reminder of the week.

We have several challenging science issues over the next four days. And we have five sessions that are distributed over that time period that outlines the discussion for the panel that's upon us. We have a full agenda for today and meeting times are approximate. Thus, we may not keep to the exact times as noted due to panel discussions and public comments. And I want to assure adequate time for Agency presentations, public comment, and panel deliberations.

For presenters, panel members, and public commentors, please identify yourselves and speak into the microphones provided since the meeting is recorded. And for panel members, we have distributed copies of overheads to be presented for today. And any public comments that are presented in written form, if we have copies, we'll be sharing them with you also for members of the panel.

In terms of public commentors, for members of the public

requesting time for public comment, please limit your remarks to five minutes unless prior arrangements have been made. And after completing your comments, we would appreciate that you complete the form that's located at public comments stand next to Dr. Bull to be used to identify yourself. If you can attach a business card that we can include that as part of the public record that would identify yourself and your affiliation.

All background materials, questions posed to the panel by the Agency and other documents related to this SAP meeting are available at docket. And the overheads that will be used for this meeting by the EPA presenters, will be available in the next few days, also on docket. The primary background materials, the agenda, the list of panel members, and the subsequent final report will be available on our docket and also posted on our SAP web site.

My role as a Designated Federal Official for the meeting this week is to serve as liaison between the Agency and the panel. I'm responsible for ensuring provision that the Federal Advisory Committee Act are met. And as a Designated Federal Official, I work with appropriate Agency officials to assure all appropriate ethics regulations are satisfied.

In that capacity, panel members are briefed for provisions of the

Federal Conflict of Interest Laws. Each participant has filed a Standard Government Ethics Report, commonly known as a Financial Disclosure Report. And I, along with our deputy ethics officer for the Office of Prevention Pesticides and Toxic Substances in consultation with the Office of General Counsel have reviewed the report to ensure all ethics requirements are met.

At conclusion of the meeting, the SAP will prepare a record as response to the questions posed by the Agency, background materials, presentations, and public comments. The report serves as the meeting minutes with be available in our OPs docket and, in addition, posted on the SAP web site in approximately. And we expect the report to be available in approximately 30 to 60 working days.

Thank you, Dr. Kendall, again, for serving as the chair and for the panel members and for the public for participating in today's meeting. I'm looking forward to a very challenging and interesting dialogue over the next four days. Thank you.

DR. KENDALL: Thank you very much, Paul. Next on the agenda, Steven Johnson, the Assistant Administration of the Office of Prevention Pesticides and Toxic Substances was going to be with us this morning. And I understand that he's got a little health problem he's dealing with at home. Ms. Sherry Sterling is here to represent Mr.

Johnson. And, welcome, Ms. Sterling.

MS. STERLING: Good morning. I'd like to say thank you to all of you panel members. You are veterans so you knew what you were getting into when you joined this panel. So I doubly appreciate what you're doing here.

I'd like to say that I realize that these four days, while they're very intensive, are just the tip of the iceberg. There's the preparation in advance and the report writing afterwards. We appreciate all of that work. This is complex. It's cutting edge and you are really helping us in moving forward on these issues.

So thank you very much. We look forward to the next four days.

DR. KENDALL: Thank you very much. It's my pleasure to introduce Marcia Mulkey, the Director of the Office of Pesticide Programs and from the Office of Prevention Pesticides and Toxic Substances. And, Ms. Mulkey, I can't say enough on behalf of your staff how they have approached this SAP time and time again to move this process forward. I think this group here that's seated is most impressed with the challenge and the opportunity to keep up with your group.

So, again, thank you for being here. This is special when we

have such high level members of the Agency join us for the opening.

MS. MULKEY: Well, thank you, Mr. Chairman. You've captured a little bit of my enthusiasm about the opportunity to be affiliated with this group of professionals with whom I'm fortunate enough to work.

You are all used to seeing me at beginning of these meetings. I like it that we are used to spending time together at the beginning of these meetings. But I did want to take a few moments to tell you that Steve Johnson who, as you mentioned, is Assistant Administrator for Prevention, Pesticides, and Toxic Substance, was very committed to being part of this particular SAP. And literally, but for bed confinement and doctor's orders, I think Steve would be here this morning not withstanding the discomfort he's also experiencing.

I have Steve's notes for his talking points which is a way of assuring that what I say, assuring me, assuring you, assuring everybody else, assuring Steve, that what I say to kick us off this morning is fully consistent with the kinds of messages that he intended to bring. So I would like to spend a few minutes on those messages. They are not extensive, but they are important for EPA and for our organization.

Starting with thank yous. A special thank you to Ron and to all

of these panel members for the time you have spent preparing for and will spend as part of this meeting and for the time you have spent at the many previous meetings leading up to this one on the subject matter that has grown into this integrated comprehensive presentation about our approach to the cumulative risk assessment for the organophosphate pesticides.

Your role has indeed been critical. I think you know that, but it does us a lot of good to be able remind you and remind ourselves how important we have found this work that we have done together. You will recognize many of your recommendations surfacing in our adjustments and adaptations in our work as we have gone along. And so it should be know surprise that we are eagerly awaiting an opportunity to engage with you in again when it is so obvious what a difference it has made in our work up until this point.

It's always helpful to us. We understand that you have the benefit of some arms-length distance from the statutory obligations, the statutory time lines, and so forth which govern, in the literal sense, our work. But it is worth reminding all of us that we do have another of the three deadlines set out in the Food Quality Protection Act of 1996 passed back in the last century.

The second deadline is August 3 of 2001 by which we are to

have completed the next 33 percent of pesticide tolerance reassessment. That means we have to have completed 6,416 of the tolerances in order to be in compliance with our obligation under law. We have been working hard since the day the law passed in order to meet these deadlines. And even more importantly, in order to accomplish the public health protections that go along with assuring that all of the pesticide tolerances of the United States meet the tough new standards of the Food Quality Protection Act.

It's clear we have been as transparent as we know how to about this fact that in order to meet this next deadline, we must have completed all or at least a very substantial portion of the organophosphate tolerances. And because this group operates by a common mechanism, that means we must have considered cumulative risk to have accomplished that.

So not only devising a workable method to assess and consider cumulative risk, but implementing it through the risk assessment, of which you now have before you our preliminary cut, is a critical aspect of meeting this August 3 deadline. In fact, it's an absolutely critical aspect of meeting it.

So we bring this to you today with some sense of urgency, and we share with you that. But we want to make it clear that while we

are committed to meeting that deadline, we are at least equally committed to doing it in a responsible way. And from our point of view, a responsible way has at least three critical elements: Sound science; transparency, openness, and understandability; and full stakeholder involvement.

While this panel and our engagement with it is an absolutely core piece of our commitment to sound science, as it happens you also play an important role in our commitments to openness and understandability and to our commitment to stakeholder involvement. This is an advisory committee complete with, not only fully public meetings, but input from the public. And that will be an element of this four-day meeting.

So you are not only a pathway through to our statutory obligations, our obligations to the American people under their laws, but to our approach to doing so in a way that we can all hold our heads up about; that is, scientifically sound, open and understandable, and involving all points of view.

With that, I want to mention that we are also looking forward to the part of this meeting that is about the public and it's input. And we, as we expect you, will be listening carefully to the perspectives, to the insights, and to the information and expertise that may be brought to

bear through public participation.

But I do want to mention that this is not the only opportunity that the public will have to engage with us, nor is it the only opportunity heretofore. But I specifically want to mention that we are conducting an open public comment process relating to this preliminary risk assessment and all of the information connected with it and that comments are due March 8. So all public commentors will have the benefit of this meeting, the benefit of the outcome of this meeting, and some time beyond this meeting in order to complete their public comments.

But I, also, want to take this opportunity to urge everyone in the public to bear the same kind of burdens we have borne of timeliness regarding this process because of the common obligations that we all have under law.

I want to conclude with just a couple personal notes. I intend to spend as much of my time as I can possibly manage to spend in the next four days here with the panel. I want to do that for several reasons. First and foremost, because I'm so pleased and gratified to be part of the EPA team that comes before you today. And I want to stand proudly with them throughout this time.

Secondly, because I learn a great deal. I learn a great deal,

frankly, from listening from to them again, as well as from hearing the input of the public, hearing the input from the panel members. And I think that that helps me do my part of the responsibilities that's around this more effectively.

And, finally, because we want to show to the public the importance we attach to this and the seriousness that we give to all of the principles I just mentioned: Sound science; openness, understand, ability and transparency.

So I'm very much looking forward to the time here and the proceedings of the next few days. And I anticipate that after it is behind us and we are on to the next step, we will always look back on this as a seminal event in the progress of science in EPA's pesticide program.

DR. KENDALL: Thank you very much. We welcome you here again, Ms. Mulkey. And it is significant when people of your level in the Agency are willing to stay with us and hear the deliberation.

I also thank you for conveying some of the comments from Mr. Johnson. It is very obvious for those on the SAP. We know that the support is there and it continues to be there. And we appreciate his support your support.

Next, I welcome Ms. Margaret Stasikuwski from the Office of

the Pesticide Programs. Margret, we've seen a lot of you and your team over the last couple years and we welcome you and congratulate you for the progress you're making. I look forward to this deliberation.

MS. STASIKUWSKI: I am pleased to be here at this really important extraordinary meeting, the review of the preliminary cumulative risk assessment for organophosphates. Today I will give some historical perspective on the development of the assessment, briefly go over the agenda, and introduce members of the EPA staff who will make presentations and participate in the discussions.

The next four days are a culmination of five years of extensive work to develop the methods and guidance for conducting cumulative risk assessment. This first slide shows the critical stepping stone documents along the way to our objective of having the first, the final, OP cumulative assessment completed in June of this year.

The first critical step document was guidance issued in January of '99 on identifying pesticide chemicals and other substances that have a common mechanism of toxicity. The final guidance on conducting aggregate exposure and risk assessments across residential, dietary, and drinking water pathways was published in 2001. The draft OP risk assessment you just received was finished

during the first week of December 2001. And our final generic cumulative guidance was just finalized in January of 2002.

In preparation for this meeting we looked back at how we consulted and sought your advice during the last five years. To get where we are today, we started in 1997 with SAP reviewing our approach to defining common mechanism toxicity for the purpose of conducting cumulative risk assessments. In March of '98, we asked SAP to review our conclusion that organophosphate pesticides form a common mechanism group through their cholinesterase inhibiting activity.

Two years later, OPs asked the SAP to review the validity of the toxicity endpoints that we selected and the approach that we used to calculate relative potency factors.

Last September, we presented to the SAP for comment our refined Preliminary Hazard and Dose Response Assessment for the OP pesticides.

For the exposure assessment, the SAP reviews and consultations covered incremental improvements in our residential exposure assessment methodology and drinking assessment methodology over the period of three years. The big leap forward in our methods took place when OPs proposed to use probabalistic Monte Carlo techniques,

first, in conducting dietary exposure assessment, then for drink water and residential assessments.

SAP reviewed several software models that were being proposed for use in exposure assessments, DEEM, Calendex, Life Line and CARES.

SAP advised the Agency several times on development of risk assessment methods for aggregating exposures across dietary, drinking water, and residential pathways for single chemicals. In 1998, SAP reviewed our probabilistic assessment methods. Building on aggregate risk assessment methods, OPs took our proposed methodology for cumulative risk assessment to the SAP in 1999.

In December of 2000, we brought to the panel the risk assessment methodology and our case study of 24 organophosphates. When you count this all up, this adds up to 21 reviews by the Science Advisory Panel of our approaches, methods, and case studies. And these all lead directly to our presentations today.

SAP recommendations have been invaluable, and here are just some highlights of their recommendations made in response to the SAP. In the area of hazard and dose response assessment based on SAP recommendations, the Agency is using a refined exponential model for dose response modeling. In the dietary exposure

assessment, OPs moved to the use of pesticide data program and other monitoring data rather than rely on field studies. OPs is using publicly available data bases and recipes in this assessment.

Based on the recommendations of the SAP, the Agency is using a finer division of age groups in children in this assessment, zero to one year, one to two years, and three to five years. This was possible with the use of the newer CSFII data with a supplemental children's survey of 1998.

In the drinking water assessment area, OPs in our preliminary assessment implemented SAP recommendations to devote resources to surface water impacts to define higher assessment tiers and develop techniques for estimating concentration distributions for probabilistic risk assessments. We adopted the recommendation to conduct regional drinking water risk assessment modeling and to shift focus for monitoring programs to support model development and model evaluation.

In their residential and occupational risk assessments, SAP made some key recommendations regard recommendations regarding frequency of children's hand-to-mouth activity and transferability of pesticide residues from surfaces to hands to mouth.

Based on the recommendations of the SAP, OPs today is using

uniform distributions for small data sets rather than rely on point estimates in residential assessment.

These are just some of the few, of some of the highlights, of how we implemented SAP recommendations in this assessment.

The next steps over the next 9 to 10 months will be to revise the December 2001 document based on today's deliberations and the public comments that we will receive. And the intended completion date for our assessment is June 2002.

Now, briefly, to go over our agenda. Immediately following these remarks, we have a public comment period that is scheduled to last through lunch and will cover all aspects of our cumulative assessment. This afternoon, Dr. Lowit and Dr. Setzer will present the hazard dose response analysis. This presentation will be followed by a public comment period and a panel discussion.

The panel discussion is scheduled to continue through tomorrow mid-morning. All of the sessions will follow a similar schedule: Presentation, public comment, and panel discussion.

Tomorrow mid-morning, we'll move to the presentation of the food exposure assessment presentation to be made by Dr. Bill Smith. The session on drinking water exposure assessment is scheduled to start tomorrow after and continue through mid-morning Thursday.

The session will be presented by Mr. Costello and Mr. Nelson Thurman.

Residential and non-occupational exposure assessment will be presented by Mr. Jeff Evans and will proceed from Thursday mid-morning until afternoon break. And then risk characterization to be presented by Mr. Dave Miller. And the session is to scheduled to continue through mid-day Friday.

I'd like to acknowledge that participants -- and these are just a few of the people in EPA who are responsible for preparation of this document. Mr. Kevin Costello, Dr. Vicki Dellarco, Dr. Elizabeth Doyle, Jeff Evans, Anna Lowit, David Miller, Randy Perfetti, Woody Setzer, Bill Smith, and Nelson Thurman. Thank you very much.

DR. KENDALL: Thank you, Margret. That was quite a summary. A lot of memories. In fact, it even forced us to change our management paradigm of the SAP because there were so many meetings that we had to rotate the chair because it was so challenging. And that has actually worked out extremely well. Our permanent panel members have stepped up and have worked with me and we have been able to accommodate this process. A lot of challenging meetings and discussion.

So here we are these years later. And we, at this point are there

any questions from the Panel for our speakers this morning from EPA? We're right on time. Any clarification? I think we're all just overwhelmed right now just reflecting on this.

We would like move into the public comment period. I have on my agenda here at least five registered.

MR. LEWIS: Right.

DR. KENDALL: We will start in the order I have received them. Jennifer Sass, Dr. Jennifer Sass, on behalf of the Natural Resources Defense Council. If you would come forward. The public commentor microphone is to our right. And we are asking -- first of all, welcome. And we are asking that those that do come forward to present try to limit your remarks --

MR. LEWIS: Five minutes.

DR. KENDALL: -- to five minutes unless other arrangements have been made. And if you anticipate it to be longer, please, approach me or give us some note. We're trying to accommodate everybody. So anyway, we will go ahead and proceed forward. State your name affiliation, please, for the record.

DR. SASS: Thank you. My name is Jennifer Sass. I'm a senior scientist at the National Resources Defense Council. I've made previous arrangements so I have about ten minutes to present.

And I want to first thank the EPA. I think they've done a tremendous job and a tremendous effort has gone into this both in the science and in the presentation in making it publicly available and making it accessible to the stakeholders in going through the presentations, which at best, are time consuming and at worse must be painful. And I do thank them. It's been a tremendous job.

And also thank the SAP. It is a tremendous commitment of time. It's also a very, very important issue. And it will set the stage for cumulative risk assessment to come by the EPA.

Onto the assessment. I have a couple points. First of all, I think that children have been inadequately considered throughout the risk assessment. NRDC requests that the Scientific Advisory Panel recommend a FQPA factor of at least tenfold be applied to account for the absence of proper developmental testing and for demonstrated neurotoxic effects in the DNT, the developmental neurotoxicity battery of tests where such tests have been done.

Under this point, all toxicology data is derived from adult animals. This data cannot be extrapolated to fetuses, neonates, and juveniles directly. It is an extremely serious omission in this cumulative risk assessment that all toxicological assessments, including dose response determinations, are based solely on adult

animals, in this case, cholinesterase inhibition of female rat brains with know experimental data from fetuses, neonates, or juveniles.

Considering the impetus of the CRA is the FQPA, which mandates the reevaluation of pesticide exposures with specific attention to the effects on fetuses, infants, and children, it is an obvious omission to disregard the life stages from the tox assessment. The magnitude of this omission, especially in light of the fact that less that half of the organophosphate pesticides have undergone DNT testing as required by the Agency is pervasive through throughout this document and is, therefore, discussed throughout these comments in various lights.

The developmental toxicity testing, the DNT, is still outstanding for a good number of the organophosphate pesticides and this critical data gap makes it impossible to assess the neurotoxic effects to fetuses, infants, and children.

Studies show that the DNT testing is more sensitive and, therefore, more appropriate for assessing and protecting children's health. DNT testing is essential for pesticides, not only as a measure of toxicity to the developing brain and the nervous system but also as an often more sensitive measure of developmental and reproductive effects generally.

EPA's task force for the 10-times FQPA, recommended that the DNT testing be included as part of the minimum core tox data set for all chemical food use pesticides for which a tolerance would be set. In fact, there is a data call in September 10 for DNT testing on all the OPs, all the organophosphate pesticides.

All of the OPs must be assumed to be developmentally neurotoxic. NRDC believes that the Agency must presume that the developing nervous system is more vulnerable than the adult to neurotoxic insult. NRDC requests that the SAP recommend that a tenfold FQPA factor at least be applied to the OPs to adequately protect fetuses, infants, and children from these neurotoxic chemicals.

Presuming all of the OPs to be developmentally neurotoxic is consistent with current scientific understanding of neurobiology, embryology, and neurotoxicology. A number of individual OP chemicals have been shown to be especially harmful to fetuses, infants, and children even at low doses. This is expected, given that the OPs are designed specifically to disrupt cholinesterase levels thereby affecting synaptogenesis, neuroid outgrowth (inaudible).

Functionally, this has been demonstrated to result in permanent disruptions in learning, memory formation, cognitive ability and behavior.

For chlorpyrifos, for example, DNT testing which was completed demonstrated evidence of neuropathology and increased vulnerability of fetuses when exposed. Most concerning in these experiments, neuropathology was seen in the neonates at the lowest doses tested. These studies were unable to identify a know effect level in the offspring in the DNT tests.

In that study, structural alterations in brain development which would result in permanent brain disfunction were seen at the lowest doses tested. Similarly, increased sensitivity of young animals compared with adults has been demonstrated with Malathion in studies performed by the registrant.

The organophosphate pesticides are a common mechanism group. They target a common enzyme and they induce a common set of effects, not overlapping but common; and, therefore, by all scientific criteria if any are shown to be phytotoxic, then it should be presumed that all are phytotoxic, particularly in light of the fact we do not have the proper DNT data on a lot of them.

Clearly, the OPs which were rigorously tested using appropriate study designs, such as DNTs were shown to be especially harmful to the developing nervous system.

The NRDC requests that the Science Advisory Panel consider all

the OPs to be developmentally toxic, both the parent compound and the toxic metabolites.

NRDC believes that any other conclusion is not supported by scientific evidence of phytotoxicity demonstrated in the DNT studies and will not adequately protect fetuses, infants, and children.

The cumulative risk assessment has failed to consider regional effects, behavioral effects, cognitive effects, and learning and memory effects in terms of neurotoxicity. The endpoints of all the tox studies used in this CRA were whole brain cholinesterase activity. This approach ignores regional variability within the brain and responses in different brain regions and masks local perturbations which may be very severe.

NRDC believes that histopathological examination would reveal regionally affected brain areas. Behavioral and cognitive testing including learning and memory tests, reflex tests, and others are key to assessing the key toxic affects of any neurotoxic or phytotoxic chemicals. Most importantly, with any developmentally neurotoxic chemicals, such as the OPs, effects are the result of more than the magnitude of the dose. Rather the effect is dependant on the dose, the duration of effect, in this case, cholinesterase inhibition. How long does the inhibition last, and the stage of the development at the which

the exposure takes place.

Exposures during key windows of susceptibility during neurodevelopment even at very low doses are most likely to have permanent devastating effects on neurofunction, including behavior and cognition. This was never examined in the current CRA and is a very serious data gap in the understanding of the toxic effects of OPs. In particular, the effects of OPs on fetuses, infants, and children have not been adequately described.

The CRA that we're going to see, the preliminary CRA, did not consider newborns, young children, and teenagers. And NRDC requests of the Scientific Advisory Panel that it recommend including all age groups in the cumulative risk assessment, including zero to 11 months, 6 to 12 years, and 13 to 19 years. This is a very serious omission, and it makes this preliminary cumulative risk assessment unable to comment on an exposure or risk to these absent age groups.

NRDC believes that these omitted age groups are the intended targets of the FQPA. And without consideration of these groups, the requirements of the FQPA have not been met.

Exposure has been underestimated throughout this document. And I think contrary to some of the cover letters that have been going around suggesting that this document is more than adequately

protective, quite the opposite. There has been an systematic underestimation of exposure and, therefore, risk. And NRDC believes that this is not a public health protective document; rather it's evidence in many ways that exposure and consequent risk have been underestimated. And NRDC details examples and request that the Science Advisory Panel consider this document to be an underestimate of exposure and recommends that EPA amends the cumulative risk assessment appropriately.

Some points that speak to that. The Agency did not consider toxic degradants. This results in an underestimate of exposure. The NRDC requests that the SAP recommend using data on toxic degradates where available, such as some water monitoring and some food data. Where such data is not available, the EPA should estimate exposure and risk based on chemical structure, mobility, degradation rate, and known characteristics of the degradates.

Though EPA has abundant data for dietary exposure to OPs, the PDP and FDA data bases used only include monitoring data for residues of the parent compound. Likewise, toxic degradates and metabolites treatment byproducts were not included in the water assessments. Where metabolites were considered, they were presumed to behave as the parent compound. This is not scientifically

justifiable. And NRDC believes that the omission of proper consideration of the degradates results in an underestimation of exposure.

Many pesticides, including the OPs, have toxicologically significant metabolites. Malioxone, the bioactivated form of Malathion, inhibits acetocholinesterase about one thousand fold more strongly than Malathion under some tests. Similarly, the dimethoxone, the metabolite of dimethoate is 75 to 100 times more potent than dimethoate in inhibiting acetocholinesterase. This metabolite is found in field crops and food.

The primary degradate of ethoparathion, paraoxone, is five times more easily absorbed than parathion and is 40 to 50 times more toxic. And one of the chief metabolites of chlorpyrifos, thixone (ph), inhibits cholinesterase more strongly than the parent. Although the metabolite appears to be short-lived, the breakdown product, TCP, is more persistent and has been found in the urine of children.

The impact of these metabolites on developing animals, even where short-lived, could conceivably have effects irreversible effects on the nervous system and heightens the need for prudence in carrying out cumulative assessments.

In this cumulative assessment, the Agency did not consider

violative residues which may underestimate expose. NRDC requests the Scientific Advisory Panel recommend including data on violative exposures. This data is available to the EPA and should be provided and incorporated appropriately.

Violative residues may be either residues detected on foods for which know tolerance is issued or which exceed the tolerance. In either case, they are extremely important and may indicate a wide spread and very dangerous problem. If residues are routinely, seasonally, or even occasionally exceeding the allowable tolerance level, then the public has a right to know and the CRA must consider these real-world residues.

It is unacceptable for the Agency to disregard these data based on actual monitoring as simply being outliers without providing evidence that they are flatly incorrect or of inconsequential health impact.

If these violative residues are the result of spray drift, of illegal applications, of machinery residues, then, again, they must be considered indicative of widespread exposure and a contributor to cumulative OP risk. In any case, the Agency must provide the data as to the frequency, spatial and temporal pattern, if any exists, and magnitude of the violations.

NRDC considers the absence of this monitoring data in the CRA to be a data gap and likely results in an underestimate of exposure.

The Agency did not consider some of the organophosphate pesticides. NRDC asks that the Scientific Advisory Panel request that omissions of OPs be considered and or else be considered an underestimate of exposure in this cumulative risk assessment.

In this preliminary CRA, the Agency has excluded from consideration all chemicals and all chemical uses which have been cancelled, voluntarily withdrawn, or phased out. In some cases, we have concerns that the phase out periods are long, four to five years. And the possibility that these phase-out periods may be extended is of concern to us.

In addition, chemicals which only have public health uses have been excluded. Again the risk to the fetus, the infants, and to the child to the developing nervous system depends on the time of exposure during development and not only the dose.

NRDC recommends that the EPA in the water assessment be based on all available data of use rates, of use patterns, and monitoring data so that the cumulative risk assessment will adequately capture the populations at highest risk.

The water model used for the preliminary CRA plots the

distribution of daily residues over multiple years and plots multiple sites rather than high exposure sites. Know point estimates were considered. This is a major departure from the individual risk assessments where point estimates were used to capture the 99.9th percentile.

Ignoring peak estimates leads to a very severe underestimation of risk and ignores the potentially devastating effects of exposure of OPs even at very low doses and even short durations on the developing nervous system.

The CRA further underestimates risk by presuming typical use rates and typical use patterns. This is a departure from the individual risk assessment which assessed exposures based on maximum allowable label rates and maximum allowable use patterns. This is a more conservative approach. While still ignoring exposures which exceed allowable limits, it at least attempts to protect those people who suffer the allowable high-end exposure. The CRA makes know so attempt.

The final output of the CRA water assessment reflects the typical or average use pattern which, although describing the majority of the calendar days, does not describe the majority of the risk.

Finally, we think that the CRA ignores the most vulnerable

populations. The effects of exposures which may be at low possibility but high risk impact are excluded from the CRA. Use of the central estimate, the benchmark dose, or BMD10, will estimate risk unacceptably. Use of the BMD01 is more protective and is supported by the data.

NRDC requests that the Scientific Advisory Panel recommend using the BMD01 rather than the BMD10 to adequately protect all populations. The point of departure in each chemical's dose response curve was determined to be the BMD10. The benchmark dose for cholinesterase activity was reduced by 10 percent. The use of the BMD10, a central estimate rather than its lower limit, ignores risk for those who are most sensitive to cholinesterase perturbations such as fetuses, infants, and children for whom changes less than 10 percent or sustained changes may induce permanent alterations in cytoarchitecture of the nervous system.

The Agency has never performed a proper evaluation of the subtle sustained or neuroregional effects of OP exposure either in the adult or in the developing nervous system. Thus, NRDC believes that the choice of a central estimate which the Agency's own data indicate is higher than the know ALs for oral, dermal, and inhalation exposure routes, is a potentially large underestimate of risk. In fact, the

BMD10 is a full threefold higher than the dermal NOAEL. And NRDC believes that the use of a lower limit, BMD01, is more acceptable as a point of departure estimate and would better reflect the low dose exposure scenarios and thus be more health protective.

Very importantly, the Agency has measured the magnitude but not the duration of the OP exposure. And NRDC requests that the Scientific Advisory Panel recommend including data on duration of cholinesterase inhibition in addition to magnitude to more accurately capture the toxic effects of OP exposure. To measure the full toxic potency of any chemical, including the OPs, it is necessary to measure the effects of sustained duration of exposure. This has not been done in the Agency's model of toxic effects.

While the animal toxicological studies considered the magnitude of cholinesterase inhibition at each dose, there is know consideration of the duration of the inhibition. Without any attempt to capture the sustained inhibition of cholinesterase activity, this model is inadequate and will likely underestimate risk.

NRDC encourages the Agency to pursue a truly expanded model which will describe not only the magnitude but also the duration of enzyme inhibition at each dose. This will surely prove extremely in evaluating the full toxic effect of OP poisoning and will be especially

important in describing the sensitivity of the developing nervous system to acute and sustained perturbations of cholinesterase activity.

Very importantly, farm children are especially vulnerable to pesticide exposure and are not adequately considered in this cumulative risk assessment. NRDC requests that the Scientific Advisory Panel recommend to the EPA that farm children comprise an especially vulnerable population and their exposure to OPs must be considered in the CRA where data is available.

Children who live on our near farms are at risk of airborne pesticide drift when they spend any time outdoors, and numerous data gathered and published reveals this to be true.

The current CRA model does not account for the leftover food effect. And NRDC requests that the Scientific Advisory Panel recommend that the EPA evaluate the overlap of peak residues which are likely to be seasonal with peak eating patterns which are also likely to be seasonal, such as eating fresh fruit shortly after pesticide applications.

These data are viable available to the EPA and should be considered. These very real exposure patterns are not random and they are likely to indicate high exposures. Of further concern, they are likely to be especially particularly concerning for young children

whose eating patterns are likely to correlate with seasonal fruit availability.

NRDC requests that the Scientific Advisory Panel recommend to the EPA that the cumulative risk assessment be based on periods of known exposure peaks such as shortly after pesticide application. In the current CRA, these data are not recorded or considered. The current CRA does not focus on the days when pesticides are actually applied.

And, finally, the NRDC believes that a nonproprietary model should be used on all risk assessments now and in the future. And we recognize the uncertainty and potential bias inherent in any model. And we request that the SAP recommend that assessments are done with the following safeguards.

Number one, that each risk assessment be performed as two or more models to begin to document model variability and model bias if it exists. Number two, each risk assessment should be performed using a nonproprietary model as one of those models in addition to any other models. And, number three, the need for uncertainty factors is required in calculating a margin of safety when probabilistic risk assessment has been done. Thank you.

DR. KENDALL: Thank you. Any clarification, questions from

the panel? Dr. Roberts.

DR. ROBERTS: Yes. Thank you, Dr. Sass. You raised many points obviously. I just wanted to ask you about two of them.

Does your organization have or are you aware of any synthesis of information that exist currently on OPs in terms of DNT testing versus adult cholinesterase as an endpoint? You've made the point that maybe by not considering effects, neurodevelopmental effects, that the wrong endpoint is being used. I think it would be very helpful for the panel, or at least helpful for me, to see a summary of the evidence, the data that exists, comparing those endpoints and the doses for various OPs to judge whether or not this is speculation or whether or not -- or to what extent data exists that support a difference.

DR. SASS: Probably the best thing out there is a paper that is still in a draft stage; although, it was a 1999 paper by Susan Makris who is a scientist with the EPA. And she compared about 12, I think, different pesticides, including some of the OPs and DNT testing with different batteries of tests that the EPA uses including subchronic. I think there was the normal neurotox, a subchronic. There is about five different tests that she compared including DNT and compared the know ALs and low ALs that resulted from these different tests and

including maternal and juvenile susceptibilities.

DR. ROBERTS: If that could be made available to the panel, I think that would be very helpful.

DR. SASS: Is that available on the web site or know, considering the paper by Susan Makris? It's an EPA paper. It's put out by the OPP. Okay. I can bring a copy.

DR. ROBERTS: Same sort of thing on the regional versus whole brain cholinesterase point. Some sort of synthesis or summary of what data exists however limited it might be that would suggest using whole brain might underestimate regional effects would be, I think, also helpful.

DR. SASS: Thank you.

DR. BRIMIJOIN: Actually, I have some direct knowledge of that particular issue. That's one of the points of interest in my research for the past 10 years. And I would say just a rough summary that there isn't a lot of regional variability. I would challenge what we just heard. There is some.

DR. KENDALL: Dr. Portier.

DR. PORTIER: Dr. Sass, thank you for making a number of points. I counted, I think, about 21. But I had a few questions. The violative exposures issue is one that's fairly interesting that I hadn't

thought about before. Do we have data on violative exposes? How often does it occur? And any idea how often it has been missed?

DR. SASS: I would answer, number one, apparently the EPA has that data and as a carrot member that has been following this all along, it's been requested by both me and the Adam Goldberg at CU. The EPA has said that they would provide that data for us. It hasn't been done yet. I know they have because they say they have it.

Chuck Benbrook has submitted comments that will be read by Adam Goldberg of Consumers Union later this morning; and he has done some estimates of that based on what he's been able to gather and suggests that in some cases it could as high as 10 percent in terms of above where these 10 percent of the exposures; it would add 10 percent to what we know. He has some charts that I can bring that I have. I think the best would be probably be to get it from the EPA.

DR. PORTIER: Well, I look forward to his comments. Mr. Chairman, if you would like to give EPA a chance to respond at this point.

DR. KENDALL: I am -- I am --

DR. PORTIER: That will be fine because I have several other points.

DR. KENDALL: Okay. Would EPA like to respond to that

particular point?

MS. MULKEY: I think what I might work best is for us, as we go through our presentation, where we have -- for example, this issue comes up in the choice of which of the PDP data we used. And so if we can keep track and rather than trying to do point by point, maybe as we roll out our presentation. Because I think there will be a number of points that the other public commentors make, also, that relate to a range of issues. So if you think that's workable, we'll try to keep track and do that. I mean, if there's some clarification we can offer that's particularly --

DR. KENDALL: I accept your suggestion. I think that would be best. Dr. Portier, any further points for clarification.

DR. PORTIER: Several. Phase-out chemicals. The comment made that some of the phase-out chemicals will be as long as five years in phase out. Is that a statement of fact or not? It's something I think we should consider in looking at this over all risk assessment. Any comment on that?

MS. MULKEY: Most of the phase outs are shorter than that. And I don't know that any of the ones that involved applications for food go that far. But some of the residential phase outs are in that range. So we'll try to be specific about that when we talk about what's

excluded as we go through our presentation.

DR. PORTIER: And then another question, again, for clarification on my part with Agency. The use of peak estimates. Dr. Sass implied that the use of peak estimates are common for other risk assessment, other risk assessments rather than the more average issues looked at here. And my question to the Agency is: That my understanding of use of peak estimates and maximum allowable use rates is more for a screening-level risk assessment than his, which I gather, is much more of a finalized risk assessment; is that correct?

MS. MULKEY: That's correct.

DR. PORTIER: And I believe that's all my questions.

DR. KENDALL: Thank you. Dr. Bull.

DR. BULL: Thank you for the points you raised. I had a couple of questions. I just didn't quite hear. Were you suggesting that the FQPA factor be applied available even when data is available or only when data is not available on the children's issue. I was a little confused by it.

DR. SASS: Right. Either when data is not available, we should presume, based on data from other OPs, that they're neurotoxic. Or when there is data available that show that the juveniles are more susceptible. If there is data to show otherwise, that that certainly

should stand definitely.

DR. BULL: The other issue I'm intrigued by as well that you brought up and it relates to what your calling violative, but it's not really violative kinds of things in the usual application of chemicals to crops and so forth. That's spills. And if there is ever an issue in the drinking water circumstance with these kinds of compounds, it relates more to spills. And I was going to bring up the issue if there has been any attempt to address how frequently that might occur. I'm not sure that it should affect any standards that are apply to applications.

But it's more likely, you know, you have a compound in commerce that's a solvent a pesticide or whatever, every once in a while it ends in up in a reservoir somehow. And those are the kinds of things I'd be more concerned about in the drinking water than the average kind of input. And I just don't know how, if there's a basis for getting at that kind of frequency.

DR. SASS: I would ask the EPA if they have a water monitoring data on that.

MS. MULKEY: Again, if we could try to fit that into our presentation on water.

DR. KENDALL: I agree. Let's proceed. Dr. Portier.

DR. PORTIER: This does bring up another issue for me as I

think about the comments I want to write down since I will miss the last two days and get some of them read before the panel.

None of the questions on the risk characterization actually ask us about the 10X safety factor and whether you want a comment on that. I won't ask you to give me guidance on that, since I'll use my own guidance on whether to tell you what I think about that. My question is will we be seeing a final version of this for comment at some later point at which point we will at least see whether you've decided to use 10X or not and then can comment on it. Do you know?

MS. MULKEY: We are working through the issue of how to analyze the 10X in the context of cumulative risk assessment and, also, the question of what kind of peer review, public participation, is appropriate. So we don't right now have a definitive time line and plan of action on that.

I will mention we have had out for extensive public process the approach for the individual chemical 10X analysis. And we expect to have our revised or final paper on that within this month. We also expect to put out for comment an approach to 10X in the context of cumulative risk assessments. That's a generic one not an application to the OPs. And that we're going to put that out for public comment in this month.

So that's been sort of the first waive is to sort through our articulation of the generic approach and then we'll be working through initially internally how we analyze that with reference to the organophosphates. Obviously, issues of uncertainty and sensitivity are the key elements of that. And there are many things in what we're consulting with this panel about that go to these questions. So there's no question that this consultation will inform our work on that, although we have not identified a very specific question relating to the FQPA safety factor.

DR. PORTIER: Thanks.

DR. KENDALL: Any further points? Okay. Thank you very much, Dr. Sass. We will continue on. We have three presenters speaking on behalf of Food Quality Protection Act Implementation Working Group, Mr. Botts, Mr. Driver, and Mr. Zabik. They've requested 45 minutes for the three of them, what I assume to be an integrated presentation or separate. Can you do it in 45 minutes?

MR. BOTTS: Hopefully, we will do it in 45 minutes.

DR. KENDALL: Are you Mr. Botts?

MR. BOTTS: I'm Mr. Botts.

DR. KENDALL: Thank you. Welcome. State your name and affiliation for the record, please.

MR. BOTTS: My name is Daniel Botts. I work for the Florida Fruit and Vegetable Association. And my real job, I direct the Enviornmental and Pest Management division of that organization which is a grower organization representing the fresh fruit and vegetable industry in Florida.

One of my unpaid jobs, among many, is being the vice chairman of the Implementation Working Group which was created after FQPA passed to provide a coordinated input into the process as the Agency moved forward to the aggregate risk exposure assessment to the cumulative exposure process to final decisions. Hopefully, it will meet the time schedules that are proposed in the law so we don't have to go through other issues associated with that process.

That bit of personal background is to provide some input on why we're here today and what we wanted to do. We did submit a series of written comments that were, hopefully, distributed to the SAP to address a lot of issues. And rather than go through those specifically today, not only are the two persons that are going to join me this morning going to make presentations, but some of those other issues will be covered in the panels appropriate to the topic matter as they go forward. And we appreciate the SAP allowing us to split those comments up, to be able to make them directly to those panels that

will be dealing with those issues.

Just in the way of general comments, I would like to echo my sentiments and more personal as both a member of the food safety advisory committee, the track committee, and the carrot committee among others. And my other unpaid job with EPA I have been involved since 1996 and looking forward to the day that we get to the point of a cumulative exposure assessment.

If somebody had asked me as a nontechnical person whether it would be possible to do what the Agency has put on the table today, I would have said it was impossible. Just knowing the little bit that I do about pesticides application, having been involved in commercial agriculture prior to going to work for the Association.

I think the cumulative assessment in the preliminary mode that's in front of us represents a significant achievement by the Agency. But having said that, there are further refinements that need to be made to the document if we're accurately going to reflect the exposures that are produced by the use, not only in agriculture, but other uses of pesticides that are out there.

To echo some of Jennifer's comments relative to the transparency of the issue, the Agency has gone a long way towards making the process totally transparent. I would suggest that I think

I've been to 80 percent of those 24 SAP meetings and other processes brought forward by the Agency to try to get to the point where we are today. And in my other life, in my real job, I'm supposed to translate that to my membership who are actually out there doing the work of applying pesticides.

And transparency, also, has an understanding component and just listening to the discussion so far and other scientific advisory panels, there's a translation to get it down to the level of understanding where my grower membership will understand the need for regulation of crop-management tools that they've been using for the last 40 years with the expectation that their use of their products had not created a problem.

From that standpoint, if we do lead to regulatory action against those products, it needs to be communicated in a manner that's understandable so when we explain it to the growers at the farm levels, they understand why they are being asked to modify longstanding agricultural practices.

The most apparent issues associated with this cumulative assessment, if you go to the CD-ROM and pull down all the data files behind the written text to look at what's there, it becomes readily apparent that this is a data-intensive process. One of my concerns

since day one has been is the appropriate data available to be able to do the type of thing we're asked to do in a cumulative assessment; and then to follow on to that from the data that is out there, are we using it appropriately. Are we looking at it in the right manner, are we taking the information that's there and utilizing it into the models and tools in the most appropriate manner.

Our written comments to the SAP, which were circulated, reflect a small level of frustration in that they are preliminary pending the results of the review of this comment will be writing extensive comments relative for the March 8 comment period to capture both what's discussed today and other issues that are being brought forward through our own internal review process. And would I hope that both the Agency and the SAP would take those comments them in the spirit that they were given. They're meant to be constructive and in a manner of continuing a dialogue with the Agency to ensure that, as we move forward to making the final discussions, we're doing it in the best possible way.

Having said that and the major points, the general points, in relation to the preliminary OP exposure assessment that you had you before you, there's some general overriding questions that I have to answer to my membership. And these are my words not necessarily the

reflection of the IWG. But it builds upon their comments.

First of all, does a preliminary OP cumulative assessment utilize the existing data in the appropriate manner. I've got to be able to tell my membership it does and understand how you got to the points that you reached.

Are the methods used appropriate to support the risk endpoints identified? If we're looking at brain cholinesterase level and using different acute endpoints to look at what drives the risk equation, if this is appropriate, how do I explain that to my membership.

And probably the last and most important to my membership, because we're the people that use these products, we are the people who are exposed both occupationally and through our field interactions and often times through being on the farm with the products as they're used, is the assessment appropriately conservative to be protective without overstating risk to the point of taking our tools away from us unnecessarily.

Having given you that general background, what I'd like to do is bring the rest of the group up that's going to be making presentations on behalf of IWG. The first will be Dr. Jeffrey Driver from Infoscientific.com, Inc., followed by Dr. Jack Zabik from Dow AgroSciences. The other participants in the process are identified on

your agendas and will come forward during the appropriate panel.

I would be happy to answer any questions, but I assume I'm not going to get nearly the technical questions that Jennifer got.

DR. KENDALL: Mr. Botts, I'm assuming that you were part of working group that developed the January 31, 2002, comments to the panel here on behalf the Food Quality Protection Act Implementation Working Group; is that correct?

MR. BOTTS: Those are the ones that we submitted on behalf of the IWG; right.

DR. KENDALL: Okay. And then the next several speakers will build on this document.

MR. BOTTS: Will build on that document, yes, sir.

DR. KENDALL: I was particularly impressed in my review of it with your summary. And I'm assuming that your additional speakers will elucidate how you came to the summary recommendations.

MR. BOTTS: I assume so.

DR. KENDALL: Any further points of clarification for Mr. Botts? Thank you, sir.

Mr. Driver. Welcome. Please state your name and affiliation for the record.

DR. DRIVER: Yes. My name is Dr. Jeffrey Driver. I am a

toxicologist by training with Infoscientific.com. We've been serving as a consultant to a variety of industry groups over the years, and I'm happy to be back for yet another presentation.

DR. KENDALL: Welcome.

DR. DRIVER: The presentation, you have a handout. I'm shifting gears a little bit so if you could just be patient with us. I'm focusing in on the residential component of the cumulative risk assessment. Some of the comments that I will make will be overarching in terms of statistical issues and other issues applicable really to dietary and drinking water as well in the overall assessment.

My comments focus on the residential and the role of one particular group, the Residential Exposure Joint Venture, the REJV, in providing critical information for doing scientifically based credible, if you will, calendar-based modeling of residential product use and exposures.

The REJV is conducting a 12-month, a temporal product use survey. This is a representative survey instrument across the United States. Thousands of U.S. households involved. It is a diary instrument that people use to record, literally, each pesticide product they use during the course of each day of each month for 12 months.

Obviously, that's an ambitious effort to maintain an adequate

sample size of participants for a 12-month period. There's a nationally recognized survey firm, NFO, a worldwide group who is conducting the survey. They have experience with temporal survey instruments.

The records that people are keeping in these diaries provide some very important critical inputs into the residential component of the modeling effort that EPA has put forth. This includes things such as the site of application, the method of application used, the frequency and timing of the use. Again, since we're doing temporal, calendar-based modeling, obviously, time is a critical element. As we said before in previous presentations, time, space, and demographics are three categories that we want to maintain consistency across individuals and within individuals in these simulations.

This survey is designed specifically for probabilistic calendar-based modeling. In my opinion, and that of the REJV, it's really required, in fact, for calendar-based modeling in the same way that CSFII you have to have some fundamental survey instrument to do dietary or drinking water. CSFII has been serving that purpose, albeit with some limitations, again with two or three diaries. But here we have an opportunity to have a 12-month diary profile for a statistically representative sample of individuals.

The survey started -- we had to go through a pilot process,

obviously. That was a three-month pilot. We started the did definitive survey in May of last year. We currently have May and June data sets that have been processed and are data based and we have an ongoing dialogue with EPA, CAL EPA Department of Pesticides Regulations, and Health Canada, regarding the results of those months that we have. So the data are coming in month by month.

Just to give you an overview of where these data fit in specifically. One of the key aspects of any residential assessment is focusing in, especially if you want to be more realistic is focusing in on which products people actually use. So when people record this diary, or fill out the diary, the key index is the EPA registration number. They record the EPA registration number of the product they're using as well as the product name. So they give us a way to check in case there's an incorrect entry for the registration number.

Obviously, with that information, you can then link it to other data bases that give you the active ingredient information, label instructions, et cetera.

The treatment interval. When you use a product, based on efficacy of the product, pest pressures that you're dealing with, obviously people may use a similar product frequently throughout the course of the year. It differs by geographic region and pest pressures

that are indicative of different regions, and the conditions that support pest populations. So that treatment interval when you think of calendar-based modeling again is very, very important.

Household-related information, what exposure scenario does it fit into. You're applying it to a lawn or ornaments or pets, et cetera. That information is captured in the survey. Obviously, getting an idea of the proportion of user versus nonuser of products in the U.S., whether it's a professional or consumer-applied product.

The use-related information. You can just go up to the right top there, Jack, and click the stop button, the left top. My apologies.

Use-related information. You can see on the slide. Demographics. Obviously, you want to understand the geographic location, age, gender, information about the household's presence or absence of children, entire profile of the household members. I had mentioned method of application. That's key, particularly, looking at applicator exposures, seasonality of the use, day of week. There are differential probabilities we find with weekend and weekday use with different product use or categories.

The next bullet is very important. I'll hammer on this a couple more times. Co-occurrence of product use. When you start looking at upper percentiles of these output distributions for cumulative risk

assessments, aggregate assessments, you start and you need to drill down and figure out what's going on. You find out that people are using more than one product not surprisingly. And while that can occur, you need to associate a realistic probability with the co-occurrence of use. And this survey estimate gives you an empirical basis to derive that probability.

The annual number of uses. That's another input that goes into this product use event allocation across the market share. Obviously, you want to accurately represent the proportion of people using the products and who those people are.

The current status. As I mentioned, the definitive survey was initiated in May of 2001. Diary results are being reported monthly, processed monthly. The May results involved greater than 14,000 pesticide applications from greater than 6,000 U.S. households. Data files are from compatible for use in CARES by the REJV member companies.

Next slide. If you could look at your handout it would probably be more meaningful than this Powerpoint. This gives you an idea of just some of the data fields that we have access to that we can process. If you look at the top, obviously, each person has an NFO ID number on the top. Starting with demographics, this example happened to be a

white female from Michigan and some associated information.

Under that is the initial inventory that this household had in place in their home when they started participating in the survey. These are the products they had in their garage and their closets, et cetera.

Then you have this application section. Obviously, they are recording the month, the day. This co-occurrence is our derivation. You can see there were three co-occurring events, if you will. There were three situations, three days. This happens to be July, August, and September. Three occurrences where more than one product was use. We know exactly which products they there, where they applied them. We can attached the associated method of application, label rates, et cetera, to derive expose estimates for this household.

This give you a feeling for the kind of information that the survey provides.

And that is my last slide. Jack Zabik will now follow-up with some work that we're doing with the CARE software that takes information like the REJV is eventually obviously is an ongoing survey. But the CARES software, we're hoping to use as a constructive tool to provide EPA and put on a cumulative risk assessment.

DR. KENDALL: Any points of clarification? Dr. McConnell.

DR. MCCONNELL: I have one quick one here. I was fascinated by your presentation. I have one question. If I were asked to do something like this, I would find it incredible task just with all the other work I have to do. How do you get people to do this? What is the incentive? How do you get them the on that 11th month to be as careful as they were the first month?

DR. DRIVER: There are a variety of features to the survey instrument. First of all, there's a screening process. By the way, there's know incentive. This is a voluntary process, believe it or not. The National Family Opinion Worldwide Group has decades of experience of doing these types of surveys. They have North America's largest pre-recruited panel of survey participants. So they have a large sort of standing group of people who, in concept, will agree participate in surveys of different durations, different purposes, et cetera. There's know monetary incentive here.

What they do, obviously, is select a statistically representative sample of these people through a screening process. We're focusing on pesticide users I should point out. You don't want to waste people's time for 12 months of the year if they really are not users of pesticides. There are some quantitative definitions of what we use to

define a user versus a nonuser.

You also, obviously, want to make sure your survey can differentiate. Are there any demographic or statistical differences between users and nonusers to make sure that you've picked people that are representative or that you know why they're different from nonusers.

Anyway, the process is the own person's interest in this subject, if you will, biases, not withstanding perhaps. But again NFO representatives have done this. They really have what they feel are statistically representative samples. What you do is you have to over sample dramatically at the beginning of a survey like this. You might start out with 15,000 house holds. At the end of a 12-month period, you may end up with only 300 who have finished all 12 months.

However, partial month or partial year people, you know, people who complete surveys, still valuable data there. If you've completed say 9 of 12 months or if you've completed maybe 3 of 12 during a high pesticide use season, you still want to look at those data and glean whatever value you can.

But what we do want for the calendar-based modeling is a static sample of a representative number of households at the end of 12 months. So you have to do some dramatic over-sampling.

DR. KENDALL: Thank you.

DR. DRIVER: That's why it's very expensive.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I sincerely hope you don't get a 99-percent dropout rate. That would be catastrophic in terms of the actual data.

I applaud the survey and the idea of doing a survey. But let me get to the practical matter at hand. What does this have any bearing on our discussions about EPA's cumulative risk assessment? You haven't shown me any examples of the real analysis of the first few months of the data. Are we going to see that?

Do any of those data violate or support any of the assumptions EPA has done? Will we see some of that?

DR. DRIVER: Well, you know, it's a timing issue quite frankly. The survey was initiated in May. Obviously, we have two-months worth of data so far. The answer is, yes, we will be sharing the information with EPA and hopefully the panel, examples with the panel. We hope that might happen at the next meeting. For us maybe at the end of April beginning of May. I think it's a timing issue.

We're trying to bring these data to bear as quickly as possible for EPA's August deadlines. There are just logistical issues in doing that.

Do we think the data are applicable? Yes, we do. We've been looking OP use that we have months for, data for rather, in May and June. We do see use of disulfoton, other compounds. So we can start to look at how the frequency of use reported and the products that are being used compared to EPA's market share estimates and the frequency.

We haven't been able to figure out exactly how EPA's assessment is estimating use across the year. We need to figure that out. And then we'll be able to use these data, hopefully, to validate or evaluate the predictions. But we're working on it. It's work in progress.

DR. KENDALL: Dr. Freeman.

DR. FREEMAN: Jeff, I was wondering whether the people who were doing the survey have it written in Spanish to reach the Spanish-speaking population.

DR. DRIVER: The Hispanic population. NFO is definitely sensitive to that issue. My understanding there is a multilingual opportunity there. I'd have to get back to you on that particular. I know the issue came up originally. I think the only demographic strata that may be underrepresented for reasons that it is in the U.S. census and other groups, might be the Hispanics and African Americans in

certain socioeconomic strata. But I can get you a response to that later.

DR. FREEMAN: Yes. The other thing on the demographics, particularly, in terms of the cumulative risk assessment that we're dealing with now, did they, also, collect the age of the children in households?

DR. DRIVER: That's correct. Yes, age and gender.

DR. KENDALL: Dr. Herringa.

DR. HEERINGA: Yes. Thank you very much. It caught my attention definitely when you started talking about population-based collection here. I have several questions.

Has NFO provide you a sample design document or a study protocol description that you could share with the members of the panel?

DR. DRIVER: I certainly will make that request.

DR. HEERINGA: I think that will be very, very helpful. The second question I had, and I think you've answered and that is: From their large prerecruited panel, which has some selectivity in it already, they have sort of stratified through a screening process intensified the sampling of people who have some propensity to use pesticides.

Is there any oversampling of farm communities, farmers, farm

families, orchard growers, greenhouse operators?

DR. DRIVER: Good question. We considered that issue. There are monetary restraints in dealing with the survey. Our goal was initially to try and be representative on various criteria: age, gender, geographic region. There are several others. But, again, getting at higher use subpopulations, we considered that but it was cost prohibitive. We figured that was a likely follow-up opportunity for individuals or other groups to sponsor surveys that focused in on those.

DR. HEERINGA: Also, if you haven't done it already with NFO, I encourage you to preserve the results of this screening.

DR. DRIVER: Yes, we have.

DR. HEERINGA: That is your only link back to the population-based activity use patterns and other data sources like human activity use pattern survey.

DR. DRIVER: That's a very good point.

DR. HEERINGA: It's going to be quite critical here because you're obviously concentrating these uses in fairly small segment of the population. It's very important, but it's concentrated.

DR. DRIVER: Very good point. And, in fact, we are doing that.

DR. KENDALL: Dr. Adgate.

DR. ADGATE: Do you know if you can use this with your own model? Is the data going to be formatted in such a way that it will be fairly easy to get this into CALENDEX as well?

DR. DRIVER: The REJV, that we're dealing with is proprietary at this point. The future of it... I think you're pointing out a very good suggestion, and I certainly agree with it. It's not my data to choose to provide it to other parties. So I think it's a good idea.

In my view, I think a survey of this type, this type of survey instrument really in the future should be conducted with Federal money in an analogous way that we're doing the CSFII. I think there's an opportunity here. If we're going to be doing calendar modeling in the future, why shouldn't be we collecting some type of survey data for residential product use in the same way we look at dietary. And that would perhaps make things publicly available in a totally transparent way.

DR. KENDALL: Very good. Dr. Bull.

DR. BULL: Thank you. Interesting project. I had one real quick question that related to some things brought up a minute ago. I notice in your list here you have a lot of products that are not OPs.

DR. DRIVER: Oh, yeah, in that example.

DR. BULL: Yeah. And the data base is apparently more useful than just OPs as well. What about these phased-out products? Are they, also, captured in here?

DR. DRIVER: You bring up a couple of interesting point. What about phased-out products? What about new AIs and their products in the future? We've contemplated that. That's part of the ongoing dialogue with EPA, CAL EPA, Health Canada.

With phased-out, with both categories, our current thinking is that we would use relevant substitutes, surrogate products, that are in the data base.

Well, let me qualify first. The phased-out products in the context of the cumulative risk assessment, they're not included, diazinon, chlorpyrifos. There are some phased-out or already removed actives that are not included in EPA's cumulative risk assessment. We wouldn't necessarily use those products unless there were substitutions. If there were other OPs that could be credibly substituted for those products's uses, then we would pick surrogates for that purpose. And the same way with new AIs. You pick surrogates that exist.

DR. BULL: I'm mostly concerned about the fact that if there's any place that the phase-outs are going to have a longer life than they

will in open commerce is in somebody's garage.

DR. DRIVER: That's a point to bring up.

DR. BULL: I've know people that have things that have been banned 25 or 30 years ago still in their garage. And it should be part of a cumulative risk assessment. My question is: Are you collecting that kind of data in these inventories for each household? If you've got that, then you've got --

DR. DRIVER: Yeah. The inventories reflect what's really there. So you do find phased-out products. I think again, you know, all modeling should be as simple as possible but no simpler. You do have to prioritize what you include in these cumulative risk assessments. I mean, in a way, you could argue this type of accounting system would give you a more accurate -- you know, you could use the inventory as is and do some great empirically based modeling and that's fine.

There are, also, practical reasons why you have to narrow down the universe of products and labels that are registered for these types of assessments. That's kind of a practical reality, I guess.

DR. KENDALL: Any further points of clarification? Can we move forward? Thank you, Dr. Driver.

DR. DRIVER: Thank you.

DR. KENDALL: Very much. Dr. Zabik, welcome.

DR. ZABIK: Jack Zabik. AgroSciences on behalf of the IWG and SSPA. I want to thank the SAP and EPA for a chance to comment. What we're here today is to give an update on where we're at with an OP case study that we're conducting using the industry CARES cumulative risk model. Go to the next slide, Joe.

And I'll share credit with those who are really doing the work on this. And I have to say that we really look at this as building upon EPA's tremendous effort. And perhaps it would be most appropriate to go back to some of the slides shown earlier of all the EPA folks that have been involved in putting together this assessment because we're really building and refining on what they already done, which is a tremendous effort.

What we planned to do with this case study is, first, a national dietary assessment. We'll first go through, or actually are in the process of going through, and rerunning the assessment with the EPA inputs. Then we're going to go back and refine these inputs using processing information which we feel is more appropriate. Also, there was a number of crops that were included that did not have tolerances for us so we'll go back and refine based on that.

With residential, given timing, et cetera, we're going to focus in

on Region 12. Region 12 represents Florida. And we're going to look at all 9 OPs used in this region. And we think this is a good region because of the intensive use down there. It's year round. Many use patterns are incorporate here.

This simulation will be based on refines inputs. We'll correct for some errors in label application rates, some scenarios that don't really exist, nonregistered uses, and also hit co-occurrence probabilities.

The methodology for CARES in this assessment will to be use a reference population which is a sample of the U.S. census. We use statistics to match to other key data bases such as CSFII.

The CARES dietary module based on 365-day profile of the consumption derived from CSFII on temporal and demography matching criteria such as age, gender, et cetera.

The CARES residential module will include product use event allocation that allows for co-occurrence probabilities and, particularly, incorporation of the data that Jeff just discussed, the REJV survey data which gives us really good longitudinal understanding.

The 365-day profiles maintain geographic, demographic. And temporal specificity. And one thing we think is really key with this

assessment is output analysis which includes both contribution and sensitivity.

Some of the software features that we think are key is the modular design. It makes it easy to adapt and expand to accommodate new methodologies or new situations required for an assessment. This includes things that we think are very important such as moving averages, being able to easily correct errors and, also, using alternative data sources such as REJV.

The data base engine for this allows for input and output data file management, so you can see what type of data you're asking and how it's being used, and has import export features.

This case study which is well underway is going to be submitted to the EPA by the March 8 deadline. And, then, it's anticipated that the CARES Version 1 software will also be submitted to EPA in March for SAP review in April and May.

One of the areas we really want to look at this morning is the whole issue of contribution analysis. If we look at this example of EPA output which is for Region 12 for children, it gives MOE result and methamidophos equivalents. And one of the key problems we find with this is not being able to determine what the key drivers are to this assessment. And, of course, without the key drivers, it's very difficult

to make risk mitigation decisions.

If we go to an example of the CARES output, shown here is an output across all percentiles by dose. We can, also, do exposure. And the key point here is you can look across the entire percentile range and then pick the percent you're interested in and drill down from there to determine what the key drivers are.

And this is important from two aspects. One is from a QA. aspect. Obviously, you want to be able to determine if there's any unrealistic scenarios driving the assessment. For instance, if you're adding up exposures and the exposures add up to more than 24 hours for a day, then you need to be aware of that. Also, it's obviously, key to be able to drill down for risk management decisions.

If we look at the next slide, this is really focusing in on a narrower band of percentiles. Again, this is looking at dose. But we could look at exposure for the different routes. And from here, you can pick a very narrow slice of the percentile to drill down even farther.

And this is really a top-level contribution look. And here you can see that we're looking at the percent contribution either by chemical, source, or route. And this the capability of this program allow us to drill down even farther. For instance, with residential,

we'll be able to drill down to what scenarios may be driving the assessment, what compounds might be driving the residential assessment, or other co-occurrence issues.

Likewise, with dietary, you'll be able to look at what specific commodities are driving the assessment or if there is a particular consumption pattern that is driving the assessment.

That really wraps up what I have to present this morning. I would like to make everyone aware that there is a web site you can look at for more information on CARES. It's alfacares.org. And as you know, there are some additional attachments that we provided to give more information on CARES.

I would like to thank you everyone for their time, and I'd be happy to answer questions or at least divvy them out to key people.

DR. KENDALL: Any questions for Dr. Zabik? Dr. McConnell.

DR. MCCONNELL: I have one question. I applaud you for instigating this exercise. But I wonder how I am to use it in my exercise this week. It's all in the future. What is in it this for me today?

DR. ZABIK: I guess this gets back to something Jeff commented on, which is timing. We have been moving we very rapidly to get the software finalized and out and get this case study

completed. The software will be available later this year. It's publicly available. And we're working to that extent to get it out. And the case study, we'll put into the docket by March 8. It really comes down to a timing thing. Obviously, we would like to have it out right now.

DR. KENDALL: Dr. Driver, you need to use the microphone.

DR. DRIVER: We're thinking that what we can hopeful do is present the CARE software, this will be the end of April, some of the panel members may not be at that particular meeting. But we will be able to share the results of the case study at that time. It's a race against time for all of us.

DR. KENDALL: Thank you. Dr. Roberts.

DR. ROBERTS: A quick question. On your case study, in terms of your ability to incorporate your REJV data, you have two months of data; is that what you're plugging in or one month or how are you going to get this? I'm wondering how you're to get this just in a couple of months.

DR. ZABIK: Yeah. I think in that case we're going to, because of timing considerations, we're going to give a specific example of how the REJV data can be very helpful but it won't be totally incorporated into this assessment. And that is both a timing and, also, this whole issue of proprietary.

DR. DRIVER: One of the aspects of the CARE software is to take the major survey data bases that are used statistically match them. Our reference population in CARES is a statistical sample of the U.S. census. Based on demographically criteria, we match those individuals to the individuals in the CSFII. Our goal is to also similarly match people to the REJV survey participants.

For purposes of EPAs decision-making, what we're hoping we can help with -- you know, summer months are peak-use seasons for some of the OPs. So we will be able to look, I think, some good examples as Jack mentioned.

DR. KENDALL: Dr. Zabik, you were, also, part of the Food Quality Protection Act Implementation Working Group.

DR. ZABIK: Yes.

DR. KENDALL: And you were part of development of the document dated January 31, 2002.

DR. ZABIK: Parts of it.

DR. KENDALL: I'd like to read this for the panel. The first sentence in the summary, "EPA has made tremendous progress along a difficult road into uncharted territory as it has developed the methodology for cumulative risk assessment and applied if to the organophosphate pesticides." Do you stand by that statement, Dr.

Zabik?

DR. ZABIK: Yeah, I think it has been a tremendous effort.

DR. KENDALL: The final sentence in that summary is, in quotes, "The sound methodology developed here provides the firm foundation for policy decisions yet to be made." Do you stand by that statement, Dr. Zabik?

DR. ZABIK: Having not wrote that statement specifically. I mean I'll give my opinion. I think that this has been a tremendous effort. But I think there are clear areas for refinement. And this is what we're trying provide with the CARES case study is looking at some of both the errors that have been made in the assessment and, also, some methodology issues and refine that and move forward and build upon what has already been done by the EPA.

DR. KENDALL: Excellent. I commend you. I'd like to one additional question. What is the level of interaction with the Agency as you're developing this case study? Is it high? Medium? Low?

DR. ZABIK: I'd say high and very good.

DR. KENDALL: Excellent, excellent. I thank you. Dr. Portier. No? Go ahead.

DR. PORTIER: Two questions. Is the CARES software, even though being public available, is source code going to be available?

DR. ZABIK: I think I'll refer that to my good friend, Jeff.

DR. DRIVER: All of the source code, the code associated with the methodology, will be available. They are third-party proprietary tools that get used in these software packages. We don't have access to the code. These are some things like graphing features and the underlying data base engine. Just like with Microsoft Access, you're not going to have access to all of the source codes. So it's not all 100-percent available, period.

DR. PORTIER: But the third-party software that are available are all general tools software like data base management, like graphics, like statistical analysis tools.

DR. DRIVER: Yeah. Everything except the data base management engine is a proprietary too. Again, I don't see that prohibitive in any means. What's real important is the code associated with the actual algorithms and the methodology to use to transform any data and estimate the output as well as the Monte Carlo sampling schemes, random number generation.

DR. PORTIER: In one of your bullets you pointed out that the CARES residential module includes a product use event allocation procedure that allows for co-occurrence probabilities. Can you give me some idea about what you mean by co-occurrence probabilities and

how you're using them in this module, especially for the example that was just shown?

DR. DRIVER: Well, if you think about a 365-day profile that you're trying to create for each individual in a given subpopulation or the overall population, obviously, there are probabilities associated with the likelihood that an individual will use a product to treat their lawn and on the same day, any given day during the year, also use a second product to treat another site, for example, ornamentals or to use the same products on multiple sites. You might mix up a batch, treat your ornamentals, your lawn.

So that's what we mean by co-occurrence, using the same product on multiple sites, using multiple products on multiple sites. Those are the things we're trying to get at. Because, obviously, you're again, trying to reach credible estimates of exposure, particularly at the upper percentiles. And I think now the 99.9 is highly controversial in the sense that we don't have robust data to support these extreme percentiles. And if we can't do contribution and sensitivity analysis to get at issues like co-occurrence, we can't make credible decision. I think we've got to be careful about.

So what I mean by co-occurrence is something someone using, again, multiple products for multiple products on the same day or the

same product for multiple sites on the same day. You need a survey instrument to derive the probability of that.

DR. PORTIER: So your co-occurrence probabilities are not, in fact, longitudinal; they are in fact co-occurrence probabilities on a single day times...

DR. DRIVER: That's correct. Except you're maintaining -- you can create a probability profile for an individual across time. So --

DR. PORTIER: I'm curious --

DR. DRIVER: -- you do get a temporal structure.

DR. PORTIER: -- longitudinal co-dependence -- co-occurrence probabilities. Do you -- have you used them in the example we're looking at here?

DR. DRIVER: No. No, we haven't.

DR. PORTIER: And if you did, how would you do it?

DR. DRIVER: We haven't yet. And as I told you, you know, this is race against time if you will. We're developing the methodology, working through case studies where we have used it. I have not shared at this presentation.

DR. KENDALL: Thank you, Dr. Driver. Thank you, Dr. Zabik. We really appreciate your comments. Mr. Botts, I just wanted to tell you, sir, when you sat down, you said you and your group would

achieve your goal in 45 minutes. And you have indeed done that, sir, and I thank you for doing what you said you were going to do.

At this point, we're right on scheduled. We will take a break for 15 minutes and reconvene at 10:45.

[Break taken.]

DR. KENDALL: Okay, we will reconvene the meeting. We are in our public discussion period. And the next registered speaker is Adam Goldberg. Mr. Goldberg.

MR. GOLDBERG: Good morning. My name is Adam Goldberg, and I am a policy analyst with Consumers Union. These comments are submitted on behalf of Consumers Union and the Institute for Environment and Agriculture. And as was eluded to earlier, much of the credit belongs to Dr. Charles Benbrook for the comments.

We have, also, submitted them in written form. But I'm sure you haven't received them yet from the EPA staff. The written comments contain additional information beyond what I'm going to present today. And they are much more expansive.

DR. KENDALL: Very good.

MR. GOLDBERG: Members of this Panel know all to well that it has been a long road to the this point -- your review of a near-final cumulative organophosphate risk assessment methodology is now

nearly final. This is your 12th meeting focusing just on the OP CRA and or the selection of an appropriate toxicological endpoint for the OP CRA. We appreciate your efforts and your durability.

While the Agency has not been able to accommodate all your suggestions and requests for more elaborate analytical approaches, they have responded well in our judgment to the most important technical recommendations and suggestions regarding how to assure that the outcome of the future OP CRA is based on the soundest possible scientific methods and data.

A measure of the major progress made by EPA over the last five years is reflected in the narrow scope of most of the questions you have been asked to address during this meeting. At last, the end is in sight for the phase of the process, leading to a point we wish to emphasize. It is time for EPA to move from the methodology development phase cumulative OP risk assessment process. It is time run the numbers and to progress to the risk mitigation phase.

We applaud for the OP risk mitigation actions taken thus far. Likewise, some OP registrants deserve recognition for putting public health before profits by voluntarily agreeing to phase out high risk residential and urban uses. But more needs to be done as is abundantly clear from a review of the results of the December 2001 Cumulative

OP Assessment.

Accordingly, we hope that your report will both provide guidance to the Agency regarding where and how it can further improve the technical foundation OP-CRAs while also stressing that the underlying methodology and data bases are sound and will support refined assessments of the relative contribution of risk from various OP crop combinations.

I'd like to briefly touch on the role of BMDs in setting the size OP risk cup. Our written comments are more expansive on this point.

Much will be said during this meeting on the Agency's proposed estimates in uses of benchmark doses. Without doubt, the last remaining critical science policy judgment EPA must make before moving to the risk mitigation phase is determining what level of exposure for children is consistent with a reasonable certainty of no harm, the basic standard imposed by the FQPA as EPA reviews existing and sets new tolerances.

This is a cautious and health protective standard. It is stricter than the benefit risk balancing standard driving EPA decision-making before August 1996. Note the standard calls for a reasonable certainty of no harm, not some level but heretofore acceptable level of harm.

Based on past Agency actions and current FQPA science

policies, as case could be made for three approaches in establishing the size of the cumulative OP risk cup and/or minimally acceptable MOEs.

One, the acute population adjusted dose of methamidophos, the reference chemical. Two, the benchmark dose for methamidophos used in establishing relative potency factors along with a standard 100 fold safety factor plus an additional FQPA safety factor. Three, a weight-of-the-evidence approach taking into account all data and knowledge of methamidophos toxicity including both its acute cholinesterase impacts and developmental impacts to the extent they are known.

The second approach was used in the analysis reported in the December 2001 methodology report, although no decision has been made regarding the need for an FQPA safety factor. Hence, the results in the December 2001 report reflect OP-CRA outcomes as if EPA decided no additional FQPA safety factor is needed. This is an extremely unlikely outcome.

We urge the SAP in the report following this meeting to offer the Agency its recommendations regarding whether and how BMDs should be used in establishing the minimum MOE that the Agency should insist upon for the child at the 99.9th level of exposure. The

SAP will no doubt get another opportunity to review and comment on the approach EPA ultimately chooses to follow.

But in the interest of reaching closure and avoiding further delay in reaching the risk mitigation phase, we hope you will speak to this critical issue in this round of review and comment.

I'd like to discuss relative potency factors for a moment. We have supported the Agency's continued refinements in its establishment of RPFs and considered the current BMD approach to be a major step forward. We understand why over the last two years the SAP has urged the Agency to move in this direction and hope the SAP is pleased now with the Agency's basis for setting RPFs.

Industry scientists have argued and may again assert during this meeting, that a 10-percent inhibition brain cholinesterase function is hardly distinguishable from natural variation or from background levels. They instead will likely argue for a BMD20 reflecting a 20-percent inhibition of cholinesterase function instead of 10 percent.

If the purpose of BMDs is just to establish relative potency factors, it would make sense for the Agency to chose a point along the lower end of the calculated BMD dose response curve for each OP that is as statistically robust as possible, hence minimizing the chances of error in the magnitude of RPFs.

Accordingly, the Agency should make a determination of whether the confidence limits around RPFs would be significantly narrower if base on the BMD20 as opposed to BMD10. We doubt that moving to a BMD20 from a BMD10 would affect statistical reliability very much. Plus, even if the Agency made the change it will mater little in final RPFs. Indeed, the Agency could even calculate an average RPF based on several points long the BMD curve. The results would be very similar to BMD10 or BMD20 approach.

While it might be defensible to use a BMD20 in setting RPFs, EPA cannot say with a straight face to the American public that a 20-percent inhibition of brain functions represents quote "no harm." It is even difficult to make this case with BMDs based on a 10-percent inhibition. And EPA should seriously consider a lower limit as has been advocated earlier by NRDC.

I'd like to turn, now, to the PDP. In CU's extensive analysis of dietary risks based on the same PDP data supporting EPAs OP-CRA, we have consistently found that just a few food pesticide combinations account for the largest share of risk. EPA sensitivity analysis lends strong further support to the conclusion that relatively few food pesticide combinations are true risk drivers and that regulatory actions targeting them can eliminate most OP dietary risk while leaving largely

unaffected the majority of OP food crop uses.

To estimate the degree of OP risk reduction achieved through implementation of the FQPA, EPA should also complete and publish an official FQPA OP baseline assessment of risk reflecting the frequency and residues found in food in the mid 1999s.

EPA decided to exclude from it's most recent OP-CRA all illegal residues found in food by the PDP as was discussed earlier during the comment period. CU has analyzed the share of total OP risk accounted for by illegal residues in PDP data through 1999. We concluded that illegal residues account for a little over five percent of total risk.

If EPA were to include these residues in future OP-CRAs, we would expect a comparable approximate 5 percent increase of risk levels across the exposure distribution. Put simply, we believe that excluding illegal residues from the OP-CRA is bad science and inconsistent with the clear language of the statute and we'd be happy to discuss at some other point, individually or collectively, the data that we've gathered on illegal residues through PDP data if it would help the members of the SAP.

Thank you for the opportunity to provide these comments. We look forward to your report and forth coming applications of the

Agency's cumulative OP risk assessment methodology.

DR. KENDALL: Thank you, sir. Any points of clarification from the Panel?

DR. BRIMIJOIN: I have a question, although I hate revealing ignorance in public. I think I've got to get clear on this and maybe somebody else does as well.

It seems to me that there are two ways to use benchmark dose data. And one is just for comparing the relative potency, the relative toxicity, of a number of different compounds. The other is the regulatory decision about what is a starting point or what is a safe level.

DR. KENDALL: Right.

DR. BRIMIJOIN: It seems to me that these two points are being grossly confused in the current discussions, both the comments we heard earlier this morning from Dr. Sass and the present ones. If that's not a confusion, if both of these individuals are correct that in going to a central measure of toxicity like BMD10 or BMD50, even, we are, in fact, recommending that this is not a harmful level of exposure and that this would be a good point, a safe dose, to regulate from.

If that's correct, that needs to be made clear to me and everyone

right now. If it's simply a matter of deciding whether compound A is 3.5 or 4.7 times more potent that compound B, then the decision should be made where do we have the best dose response date, where can we make the tightest analysis. And we don't need to pick particularly low dose just to make people feel comfortable that, oh, we're picking a dose that's nearly safe.

DR. KENDALL: Right. Good point. Mr. Goldberg, would you to address that point or question?

MR. GOLDBERG: Well, as one of the previous commentors said, I'd love to be able to turn this to somebody who is a little more knowledgeable than me. So I'd like to ask Jennifer to address this.

DR. BRIMIJOIN: Actually, I think somebody from EPA ought to comment on this.

DR. KENDALL: I am going to ask EPA would they like to respond. Margret?

MS. STASIKUWSKI: Yes, I will ask Dr. Vicki Dellarco to respond to the question.

DR. KENDALL: Thank you. Dr. Dellarco.

DR. DELLARCO: We've had a lot of discussions about the benchmark response level that we might use for this class of common mechanism chemicals. When we first went to the SAP back in 2000,

September 2000, we had to use the ED50 as some of you who were there remember that. And then when we went back and we got Dr. Setzer involved in the modeling, we brought forth the concept of using a slope scaling factor, the M value. And there was a lot of discussion at the September 2001 meeting about the use of M for looking at -- and I'm talking about potency right now, comparing potency. Or maybe going down and using a benchmark 10.

And I believe there's some written comments about using a benchmark 10 to compare potency, and we decided it was the best way to go because of the issues of parallel dose response relationships. So we wanted to go as low as we could reliably to estimate potency in an empirical range of observation. And this, also, happens to be the same benchmark response that we'll use for the point of departure.

That doesn't mean that will always be the case. But for every cumulative assessment that we do, the benchmark response we might use to compare potency may be very different from the point of departure. And in this case it is. There's been a lot of discussion and thought on this.

Do you have anything to add, Anna or Woody?

DR. KENDALL: Dr. Bull, I think you're first.

DR. BULL: This is just a point of clarification and don't

necessarily need to have an answer right now. But I'm a little confused by this issues we're addressing in cumulative risk assessment by compounds that have common mechanisms and then dealing the FQPA factor which is adjusting for some effect on development. And maybe somebody can educate me as to whether cholinesterase inhibition always leads to developmental delay or some compounds that are organophosphate pesticides also have developmental toxicities because I don't see how you combine those two, if, in fact, the mechanisms for developmental toxicity and cholinesterase inhibition are not related. And there are certainly possibilities of that occurring.

So if someone can tell me that every cholinesterase inhibitor at some level of cholinesterase inhibition causes developmental delays or other reproductive toxicities, I'd be really tickles to know that. But I don't know that off the bat.

DR. KENDALL: Dr. Harry, do you want speak to that briefly? This point keeps coming up. We've been challenged this morning -- Dr. Dellarco, do you want to comment. Dr. Durkin, I have not forgotten you.

DR. DELLARCO: Usually about the sensitivity or susceptibility to this class of pesticides has come up this morning twice. And the issue about the children's safety factor, the FQPA 10X fault factor

that's under the law. And we will be conducting a separate analysis, pulling together. We are currently pulling together data on cholinesterase inhibition that's been conducted with in utero exposures as well as postnatal exposures. And we will be looking at that and comparing it to the adult data that Woody will be discussing today.

And so the analysis that you'll hear today about looking at relative potency and the point of departure is focused on the adult animal studies. But we will have to do this analysis. And as Marsha indicated and Margret pointed out, we've taken a very careful step-wise approach to get to where we are at today in laying down guidance documents and tools.

And as Marsha pointed out, we will be putting out our final guidance for how you make a decision about a kid's safety in looking at the issue of sensitive and susceptibility in single chemical assessment. That should come out soon. And following that, we will have separate guidance on how you do this in a cumulative assessment where you're focused on a common effect and common mechanism. And we'll put that out for public comment.

So there is some literature on this. And some of these OPs do show some sensitivity. That's been published. And some of them don't. So we're going to have to look at this in total and see what it

means in respect to the group.

With respect to the susceptibility, I believe that's the issue you raised: What kind of effects can you get in terms of developmental delays and effects on cognitive function? We don't really know. And Dr. Brimijoin can probably speak to this because I believe he's done some work. But Acetocholinesterase is an important neuromodulator during development. It is an important mechanism to look at when you're looking at sensitivity and susceptibility.

DR. KENDALL: Dr. Harry?

DR. HARRY: I think you answered a number of the questions in which the framework to consider in what we're talking about this week. And I think when a number of the comments came up about referencing to the developmental neurotox guideline tests, the answer of saying, one, this is focused on the adult; and, two, that to look for the components for the children's susceptibility is the next step. We need to remember that framework as we're going through today.

I think you're going find it very difficult when you start trying to do this in developmental. One of them is going to be there is a good amount of effort and a good amount of data on the adult. We still have to come in -- I still come in with a question of what's adverse. And you're going to have that even more when you get

developmentally. We're not going to have that data in the developmental. We're going to have made an awful lot of assumptions based upon the adult data. And I think you're going to need a lot more data and understanding of the basic biology of that to be able to truly make these different.

The other caution I would raise in there of automatically assuming that the developing animal is more sensitive than the adult based upon the two testing guidelines is that your developmental neurotox guidelines are much more intensive than the adults are. You deal with a cognitive functioning. I don't know how much you have on organophosphate on the adult on cognitive functioning or learning component. But you do have that in the developmental.

And you have a number of other components of the developmental that we're sort of still waiting on data on for some validation of those. And that's what was brought up with the Makris Study that 13 chemicals have been triggered. It was still in question about how much more sensitive that testing guideline really was for picking things up.

So you got a lot of other things involved in that developmental aspect that you're going to have to work out before you even get to this point on it. Just to raise a caution on that.

DR. DELLARCO: Let me just since you mentioned the Makris Paper and that came up this morning. That paper wasn't really intended to look this issue sensitivity and susceptibilities to OPs. And although it was mentioned that the Panel may want to look at it, we'll be more than happy to provide it to you. But it's not really going to get at the heart of the issues on this.

DR. KENDALL: Very well. Dr. Durkin.

DR. DURKIN: Just briefly, there was a point made about the two uses of the benchmark dose; one is point of departure; the other for relative potency. And I think I heard Vicki say that in some cases you may use something like an ED40 or whatever for relative potency and an ED10 or ED1 for a point of departure.

The one thing I think you have to keep in mind with the OPs and any extrapolation of this method to other chemicals. If you have a dose response function or a class of them where potency is constant across doses as in what you had originally done with probative analysis, then it doesn't really matter where you measure the potency, although the variability of the relative potency can vary.

With the OPs, especially the kinds of much more complex model that you have now, relative potency in that sense is no longer a meaningful term. Relative potency will vary with dose. So for the

OPs, I think you are in a situation that once you decide on your benchmark dose, be it an ED10 or ED1 or whatever, that is indeed the dose or the response level that you have to use to define relative potency. So that at least within the context of your point of departure, relative potency is indeed the ratio of equitoxic doses. And as long that isn't violated, you're going to be fine.

But I think you have to be a little careful about talking about using some other region of the dose response curve for the kind of model you have now, even though your confidence intervals might be narrower, that measure of relative potency would not be appropriate for the point of departure that you may have selected.

DR. KENDALL: Good point. Any further points of clarification for Mr. Goldberg. Thank you. Thank you, sir. Dr. Portier.

DR. PORTIER: Just to make it clear that we've had two sort of disjoint comments about the use of relative potencies and the point of departure. And I want to make sure when we get into the Panel discussion, we get back to this because I may or may not agree to either one of the two.

DR. KENDALL: I intend to do that.

DR. PORTIER: I think that's something we have to discuss.

DR. KENDALL: We intend to do that. I didn't it's appropriate to do that resolve that right here. It's on the table. I think we understand.

We've have had one additional presenter that would like to approach the Panel. Ray McAllister.

MR. MCALLISTER: My name is Ray McAllister. I am the vice president for Science and Regulatory Affairs for Croplife America. In my work with the Implementation Working Group, it was my responsibility to coordinate the assembly of the written comments which we submitted to you. And I felt it was important to take just a few moments and respond to Dr. Kendall's question earlier on the summary statements and those comments.

He asked specifically about the final statement, "Sound methodology developed here provides the firm foundation for policy decisions yet to be made." Our comments were assembled quickly. And even when you have the opportunity for a lot of people to review, it's not unheard of that someone else reads it and finds a different way to interpret it.

What we intend by that statement is that the sound methodology that comes out of the cumulative risk assessment process that is being developed now must provide a firm technical foundation for policy

decisions yet to be made. The development of sound methodology is the responsibility of EPA as well as a number of other contributors including in a large part this Panel that the Agency has consulted and also the stakeholders who are involved in providing the data that goes into the risk assessment and who are involved in helping the Agency with interpretations of that information. And that was our intention with that statement.

DR. KENDALL: Very well. Any points of clarification for Mr. McAllister? Thank you, sir.

At this point, are there any other persons desiring to approach the Panel in the public comment period? We allocated an extraordinary amount of time to try to accommodate this. And I was concerned in the early phase of this because I didn't know if we could get through it, but we've moved very quickly.

DR. TOBIAS: Abraham Tobias with Adventis Cropscience.

DR. KENDALL: Welcome.

DR. TOBIAS: In the discussions earlier there were questions asked whether there were data concerning spouse and children on the farm. I'd like to remind the Panel, and maybe to inform the Panel that under Croplife America and several companies within that organization we are running a study. This is a companion to the NCI study which is

looking at cancer risk for the farmer, their spouse and children. We have done a study. We are in the final stages of completing that study where we will get to the issue of what children and spouses are being exposed to.

From our preliminary study, range finding study, we're not finding much exposure to those subpopulations. And I think our final study will bear out that information and will give the Agency much more information on that front to be able to say that the exposure is very, very minimal or nonexistent. I just wanted to bring up to the Panel that we will be coming up to the table with more data.

DR. KENDALL: Excellent. Is this regional based or national based?

DR. TOBIAS: It's paralleling the study that is run by NCI which was done in Iowa and South Carolina. Excuse me. North Carolina. We mimicked that study, and we mimicked the questionnaires, the epidemiology aspect. If you're going to get into the epidemiology questions, I'm the wrong cowboy to answer those question. So I can't answer those.

DR. KENDALL: We thank you, though, for updating us, Dr. Tobias. Dr. Portier. Just a minute, Dr. Tobias. Do you have a question for him?

DR. PORTIER: Yes.

DR. KENDALL: Dr. Tobias, can you reapproach the microphone. We have Dr. Portier with a question.

DR. PORTIER: First of all, I'll play nice, Chris. I'll point out that the pesticide study is both NCI and NIEHS just to make sure everybody hears that.

DR. TOBIAS: I apologize. I didn't meat to slight you or anybody else. And it is part of EPA, too. I better apologize to them for making that error.

DR. PORTIER: More importantly, do you have any preliminary data to show us now?

DR. TOBIAS: We're in the final.

DR. PORTIER: Actually look at quantitative numbers and make --

DR. TOBIAS: Yes. We're in the final stages of doing the QA aspects on a lot of these numbers. And plus checking our field checks and everything else so that before we come out with some preliminary information that we, at least, are on a solid basis from the analytical point of view. So we will be ready to give some preliminary information out on that shortly. I can't promise you what date or time.

Let me just plead a little ignorance. I haven't been in touch to

that for the last month due to some personal things, so I have to bring myself up on to speed on a lot of the issues that we're working with that right now. I am the treasurer for that group, and they do want me to sign some checks. So I will figure out a lot of things.

DR. PORTIER: So in terms of our debate this week there's nothing for us to look at.

DR. TOBIAS: I can try to get you what we did in the preliminary study, our range finding study. And I think we may have some data from the first year of the study because it was a two-year event. We looked at it over two years. And we wanted spatial and temporal issues on the study. So, yeah, I may be able to get some information to you. But I wanted to make sure the Panel did know that and Agency will get that information.

DR. KENDALL: Thank you very much. Dr. Conolly.

DR. CONOLLY: I guess this is a question for the chair as much as anything. We've heard a number of presentations this morning about I think very important studies that are underway, collecting data, which obviously could impact cumulative risk assessment for organophosphates. And we've also heard question about whether information is available in a way that actually let's us usefully evaluate the assessment that the Agency's presented to us or will be presenting

to us over the next couple days.

What I may be looking for is a bit of guidance here about what our job is. You know, in risk assessment, those of you who have looked at the cancer guidelines recently, for example, it's carefully laid out there how there are default approaches to risk assessment which can be carried on with minimal data sets and much more complicated approaches that require rich data.

And I think we seem to be faced with a similar situation here where we have a methodology that can go forward with currently available data and alternative approaches that will require much richer data sets and which might not be doable today, might be doable in a year, or two years or five years.

I think it's important that this group be clear on what it is we're here to evaluate today. Is it sort of this richness that might be pursuable in the future or looking just at what's on the table today and, you know, what the Agency has to work with today?

DR. KENDALL: I'd like to ask Ms. Stasikuwski to respond to that. Margaret.

MS. STASIKUWSKI: Yes. In my presentation, I described our obligations under FQPA. And we are discussing today the preliminary risk assessment that we need to finalize in the summer of 2002. So we

are discussing that which you have reviewed, and that's the crux of the discussions this week.

DR. KENDALL: What I see happening, Dr. Conolly, there additional projects underway that can contribute to, additionally validate, and make this whole process more robust I believe. So, again, this is a continuum we're working on. Yet the Agency has certain time lines they've got to respond to and I think our job is to continue to offer and contribute to the acceleration of their efforts to bring the preliminary cumulative risk assessment to the table. And I think they're doing it.

I'd like to ask the EPA -- at this point, this will close the public comment period. And I'd like to ask, and we are ahead of schedule. And we're significantly ahead of schedule. So I'd like to ask the EPA, would you like to procedure with your introductory comments from Dr. Lowit or would you like to go ahead and take our break.

MS. STASIKUWSKI: Just consulting Anna. Are we ready?

DR. KENDALL: The Chair would like to take our break at 12 noon, therefore, we have 45 minutes. Would you like to engage us for the next 45 minutes?

MS. STASIKUWSKI: We're just consulting on time.

DR. LOWIT: We might run a little long but too much longer

than 12.

DR. KENDALL: Would you like to proceed or we could reconvene at 1. I'm a little reluctant to reconvene. I think a lot of people, Dr. McConnell questioned the point of view of start at 1. I'm afraid people may be traveling in to see the dialogue beginning at 1:30. I would like to ask if you can start and I would like to stop at 12 noon.

DR. SETZER: Well, actually, my only concern was that at 12 noon I might have 10 minutes left and a couple of three slides.

DR. KENDALL: Okay. Then let's do it. Dr. Portier.

DR. PORTIER: I'm going to propose differently in that because this is such an important topic and because people may actually be traveling here at 1 o'clock, not only to hear public comments, not only to hear the Panel, but also to hear EPA's comments on what they have done in their defense of this. I would move unless we have more public commentors or a specific topic we want to discuss now about the approach we are going to take to reviewing this that we close this session until 1 o'clock as stated in the calendar.

DR. KENDALL: It's 1:30. I would --

DR. PORTIER: I know it puts us potentially in a tight spot this afternoon. But, again, this is a very complicated risk assessment, it covers a number of issues, and I'm a little bit concerned about us

moving too quickly on it.

MR. LEWIS: I think just managing the time, I'd like to comment. I'd really like to see us use the extra hour we have because we do have a tight agenda. And we have notified everyone that this is a flexible schedule, that with the complexity of the issues being discussed and the public commenters that they have to be prepared that it might be 1:30; it might be 1 o'clock; it might be 12 o'clock; it might be earlier.

So I understand your issue, but I've also very concerned that we do have the time. And I think we're going to need if today, so I'd like for us to try to use it. Thank you.

DR. KENDALL: All right. Let's proceed, EPA, and we will reconvene at 1:30. Let's go ahead. That way we will attempt to address Dr. Portier's point of view of people traveling in if they can't get here until 1:30. Let's go ahead and try to move there are your presentation. Is this okay, Margret?

MS. STASIKUWSKI: Yes, we're ready.

DR. KENDALL: Very good. Thank you. Let's proceed.

DR. LOWIT: As we look at time, I'll try to go quickly so I can concentrate on what Dr. Setzer is going to talk about. I'll reiterate the same appreciation to the Panel that you heard and will hear in the next

few days.

In 1999 the Agency released a document identifying the organophosphates a common mechanism. And, subsequently, we have concentrated on the inhibition acetocholinesterase as the endpoint for the cumulative risk assessment.

The hazard and dose response portion of the assessment has been to the Science Advisory Panel now three times. The first time in September of 2000, followed roughly one year later with a preliminary hazard and dose response assessment, which we'll call the July Document. And what we'll discuss today is the revised preliminary hazard dose response assessment which we'll call the December document.

The hazard and dose response assessment includes 29 OPs that have exposure through either food, water, and/or residential and ongoing as a determination of roles of potency for 3 more: chlorethoxyphos, profenofos, and phostebupirim. Just to remind everyone, to put it in context, we are using the relative tox potency method where each chemical is compared to an index chemical and we are using methamidophos as the index and exposure equivalents as you'll hear in the next few day, of the index chemical are combined in the assessment.

The toxicity data used in the assessment come from oral, dermal, and inhalation studies tested in rats of subchronic and chronic exposure, and the exact same data in the July Document was, also, used in December. And just for reference, the electronic data set of all the oral cholinesterase data and not only the brain compartment but the plasma and red blood compartments is available on the internet.

We're going to concentrate in the next hour or 45 minutes on four key major refinements. One was the relative potency factors used in the preliminary assessment, the method for combining the cholinesterase data molding of the low dose region of the dose response curve, and also the measure used as a potency determination.

In the July Document, male red blood cell cholinesterase was proposed as the end point. Red blood cell cholinesterase inhibition will continue to be an appropriate endpoint for risk assessment. But RBC was selected primarily based on the availability of a large data base and our ability to consider time course information. And the males were selected over the females for not a very good reason.

In the December Document, the female relative potency factor is based on female brain cholinesterase inhibition were used. And why was the brain used? All though red blood cell cholinesterase is an appropriate end point for risk assessment, the confidence limits on the

potency estimates for brain were much tighter than those of red blood cell. Also the brain is target tissue for OPs.

Why were the females selected over the males? The sexes were equally sensitive for most of the OPs with the exception of roughly five for which the females were more sensitive. And this is my rode map sign to turn it over to Dr. Woody Setzer who will discuss the methods used.

DR. SETZER: Good morning. I thought I was going to be saying good afternoon.

In this talk I want to do essentially four things not with equal weight. First of all, I want to review the methods that were used in the July draft and bring you up to speed and remind you what we did before and what you all commented on and talk, briefly, about the issues that were raised in the September meeting that we addressed in this analysis and tell you that how we addresses those issues; and, finally, since release of the December Document, I've done work since then and I'll talk about that as it's appropriate during the discussion.

Overall, the SAP supported the approach that we used. In particular, they were happy with the exponential model using multiple studies and time points. And I was happy to see accommodation for using open source software package to do the analysis to facilitate the

communication and oneness of the analysis.

It was recommended that we look further at the low-dose end of the dose response curve in response in part of some commentors at that meeting. And there's a comprehensive list of all the comments in the cumulative risk assessment available at the web site indicated there.

Just to remind you, in the July Document, which the September SAP commented on, was based on a dose response model expressed here. It was essentially an exponential model with a modification to allow us to estimate an horizontal asymptote. And we were using what we've been calling the dose-scaling factor as a measure of potency in that analysis.

In July, we followed a strategy. We have multiple data sets. And so you've got to figure out how you're going to get a single estimate out of multiple data sets for a given chemical. In July we estimated a value of potency for each individual data set and then used a statistical approach to nested to essentially a sort of a population model to nested data to estimate an overall mean potency.

And the point of this slide here is to indicate that what we have are sort of major studies with individual data sets nested within those studies, and then what we're trying to do is estimate an average

potency, sort of an average of those studies.

Finally, to estimate the parameters for the model in the July Document, we used an approached called generalized least squares. We assumed the constant coefficient of variation. What that means is variance, within group variance, was presumed to vary according to square of the mean. This is a sort of situation where scientists like log transform their data or when they express variability, they like to talk about coefficients of variation instead of standards deviations.

That's a common. That's a common sort of structure to find for these biochemical data and that was the weighting scheme we used in that analysis.

Also used a sequential approach to fitting. And the reason for this was it wasn't always possible to estimate all the parameters to the data. And, also, we found that occasionally we didn't get -- we weren't able to describe the data with the model given.

The first step was to fit the full model to all the data. And then if we didn't get convergence or estimates to all the parameters or the fit was inadequate, we would repeat the following process. First, set the parameter that quantified the horizontal asymptote to zero, refit to the data set. If it still doesn't work, drop the highest dose and keep going until you run out of doses or you get a good model.

Here are some problems and issues from the September SAP report. First of all, the approach we used to estimating the horizontal asymptote could result in bias estimates. Remember, we're setting B to zero if something doesn't work right. It turns out that N is sensitive to that estimate of B. So if we base our potency estimate on N and set B to zero, you're potentially introducing some bias.

It was suspected that the weight function used underestimated the variance at low doses and overestimated at high doses. So we needed to revisit that decision.

And, finally, the dose response curves for some chemicals appeared to have a shoulder at low doses; in other words, it didn't drop straight down like an exponential model but was more horizontal for a range of doses before the curve steepened. And we wanted to try to address that.

The changes I want to talk about today. First of all, we changed the way the models were expressed in terms of the parameters. We reparameterized the model. It's essentially the same model we're using; we're just expressing it in terms of different parameters that make the model a little bit easier to estimate.

Secondly, use the reciprocal of the benchmark doses as a measure of potency instead of m as recommended by the SAP. That

has several benefits. One of them is that the benchmark dose turns out to be substantially less sensitive to the estimate of the horizontal asymptote than is the potency. So we're winners there.

And, finally, rather than fit a model to each individual data set and then combine estimates, we combine the data sets and then fit what's called a nonlinear mixed effects method -- and I'll talk about what that means before I stop talking anyway -- to estimate that model.

One of the problems -- the issue of setting B to zero and then going from there, it was one of the probably two potential sources of the bias in the last estimate that we could relatively easily address. One of the changes we made in this analysis is to use a profile likelihood approach to estimate a value of B that's consistent with the data when we can't estimate is jointly with the other parameters.

The goal there is to identify a value of the horizontal asymptote, well, like I said, consistent with the data. It's plausible. And then condition the analysis on that value.

One of the consequences of adopting of strategy of fitting models to a number of data sets was we have more dose levels available and it's a bit more possible to develop a model to describe the low dose shape of the curve.

We also changed the weight function. We set the weights to be proportional to the mean value and not the squares of the mean value. That seems to improve the sort of the scatter of the residuals plots. And I'll talk about the more when I give dose-specific detail.

Okay. Let's go through the models, the various forms of this simple model. At the top, I show you the July model we started off with. It's perhaps easiest to understand this first reprioritization in terms of the units involved. This first model we have parameter B and a parameter A. Both of them are in terms of response units. And, actually, partially in response to some confusion that happened among the discussion in the September SAP, it made sense to reparameterize the model to pull out one parameter that contained units in terms of response units, factor that parameter out, and A then has always been the background or the control estimate of the control cholinesterase activity level.

And then there's this parameter P sub B which is a fraction that ranges between zero and one. Makes it a fraction. Which is just this ratio B over A. So instead of estimating B and A, we're estimating A and the ratio of B over A. Same model, just a different approach.

And then, finely, and this is something that I've done since the December release. This looks much more complicated, but it's not

really. It's just algebraically more complicated. We have, again, the same model but instead of using the slope parameter m, scale parameter m, we reparameterized the model in terms of benchmark dose. And in all the calculations, we've set benchmark response level to correspond to a 10 percent reduction in mean cholinesterase activity.

The main advantage of this is that the estimate of B and D, as we said before, tends to be substantially less dependent on the estimate P sub B. So when we do estimates with this model, we're somewhat more stable numerically.

Advantages of the current model, more stable estimation. And it, also, simplifies computation of the benchmark doses and standard errors since it happens in one computation instead of two.

And just to keep me honest, the parameters we actually estimated were the log of the parameter A, the log of the benchmark dose, and this logistic transform of P. Those are mainly to assure during the estimation process the parameter values stay legal because the software that I was using doesn't allow to put bounds on the parameter estimates correctly. At least not easily.

The model fitting. We use the approach called nonlinear mixed effects models. This is really a rubric for a whole suite of different

approaches to dealing with population models. The particular approach I used the is codified in a function N, L, and E in the software package R. It's based on an approached developed by Doug Bates and his coworkers. And Doug Bates -- well, who is also the author of the software package.

Essentially, the approach is this. For each parameter that we're estimating, we assume that there is a separate mean value. And in our case, for example, for the background level, we assume there is separate mean value for each sex by unit combination.

Let me digress for a second. What I mean by that is not all our studies used the same units for measuring cholinesterase activity. And it's not always obvious that you can just do a simple conversion to get from one unit to the other because they imply somewhat different methods for measuring cholinesterase activity. It made more sense to keep those sort of separate approaches separated out. And then we estimated a separate value for B and for the log benchmark dose for each sex.

Superimposed on that, we have multiple studies for the same chemical and multiple data sets for each study. And we treat the parameters. We treat each of those sort of individuals levels of the nesting, as if they had their own mean parameter level and they vary

around. So for example, the mean value for the studies varies around the overall population mean level and the mean level for the individual data sets vary among the mean level for the study. And this is, essentially in somewhat nontechnical language, this is the approach that LME uses.

And, finally, as I said, before, we've used weights based on presuming that the error variances were proportional to means. This is determined empirically. It seemed to work better. It seemed to describe the variation better than did the previous weight function.

We still had problems with getting --

DR. KENDALL: One moment. Dr. Portier.

DR. PORTIER: Simply a question of process for this. Again, this is a fairly complicated analysis that we're looking at and Dr. Setzer is about to go from the description of the model to the description of the methods used to estimate parameters in the model. And I'm wondering if this is maybe not a good point to stop and have questions for Dr. Setzer before he goes onto, again, more complicated and other issues or not and whether my colleagues feel that is a good idea or not.

DR. KENDALL: Dr. Heeringa.

DR. HEERINGA: Just a very quick clarification to this point.

In terms of random effects in the nonlinear mixed model, you're effectively nesting data sets within studies.

DR. SETZER: That's correct.

DR. HEERINGA: So you've got a nested random error term there. Okay. Just as a little bit of background for me in terms of the numbers of observations we could typically find at each of these levels of nesting at any given data set for a study would have multiple dosing. Would it have replications at each dosing?

DR. SETZER: I'm sorry. There were probably slides from the previous presentation I should have included here. Each individual data set is a complete dose response study. It would be typically three, four occasionally five or more doses at each dose group. You'd have anywhere from 4 to 10 animals. And actually the data reported to us are in terms of means and standard deviations from those studies.

DR. HEERINGA: Means and standard deviations across animals for each dose level.

DR. SETZER: That is correct.

DR. HEERINGA: And then separate data sets for each study if they replicated it.

DR. SETZER: I'm sorry. Yeah, right. The separate data sets normally correspond to different durations of exposure.

DR. HEERINGA: I see. Thank you.

DR. SETZER: So the study would have been, for example, potentially a chronic study, the number of animals that have gone on study. There would have been serial sacrifices during that. We're talking about brain cholinesterase here so the same animal can't be observed twice.

DR. HEERINGA: Thank you very much.

DR. KENDALL: Thank you. Dr. McConnell.

DR. MCCONNELL: As I understand this, you have multiple data sets and you combine them in your analysis. Do you have minimum criteria, or do you have criteria to say this data set is good enough to use? Or do you take any data set and, because there are some numbers there, you use it?

Where I'm heading is that in any area of science we all know that some data sets are better than other data sets. In fact you might, in looking at five or six data sets, find one of them to be particularly outstanding, one of them to be minimally acceptable. Are all five of those from the minimally acceptable to the outstanding one given equal weight in your analysis?

DR. SETZER: I suppose that's a difficult question to answer completely. Probably the answer is no for two different reasons.

There was some filtering that went on before we even looked at the data. And we talked about this for the September meeting, that there were minimal standards in terms of adherence to the standards in terms of performance of study and being able to extract the relevant information from the study in a believable way. There were minimal criteria that the study had to ask before I even saw the data.

Secondly, in terms of the actual sort of statistics, one criterion for quality of a study is sort of how tight the data would be for a given dose level. And in general, a study where the data are quite variable will be weighted in a not a very obvious way but be weighted less in the final estimate of the mean than would be a study that had a much tighter estimate of the same value.

So there is some weighting going on based on data quality to the extent it's expressed in terms of a sort of variance and things like that.

DR. MCCONNELL: I think I understand.

DR. KENDALL: Any further points of clarification that really can be held to the completion of the presentation, you think we need to do it now. I mean, Dr. Portier made a good point. If there is a clear need to get definition as to the methodology versus the process, you know, let's do it. If not, let's proceed.

Okay. Dr. Portier.

DR. PORTIER: I promise. I only have two questions. The first one has to deal with the simple model versus the broader model. Obviously, the broader model, if I'm looking at my notes, goes to infinity effectively converges to the simpler model. Is that --

DR. SETZER: That's the model we've called the expanded model. That's right.

DR. PORTER: Well, as S goes to infinity or as D goes to zero. That's where they become collinear is either at infinity or zero. There's no way to tell the difference.

DR. SETZER: Yes. Well, yeah, effectively, it's the same model. Yeah.

DR. PORTIER: And you've done a number of conversions from arithmetic numbers to log transform parameter estimates, those of which will affect, obviously, not only the parameter estimates themselves but any variance estimates that you put on those parameters. Specifically I'm interested in the parameter PB and its inability to assume a value of zero when you do a log transform to estimate PB. When you go into the estimation phase, we you tell us how you dealt with that issue specifically? It pertains to the other parameters as well, but PB bothers me a bit.

DR. SETZER: Yeah, it's true. We can't get zero, but we can

we can get something very small. And, in fact, I haven't done anything special with that to deal with the possibility that P sub B can get very small.

DR. PORTIER: In your convergence criteria, then you have a minimal value in essence of PB that convergence is going to stop on, or log PB, negative value in log PB, upon which it will stop then because obviously negative infinity is something the computer can handle easily.

DR. SETZER: That's right. It sort of runs out at 10 to the minus something, 320th or something like that.

DR. PORTIER: Thanks.

DR. KENDALL: Dr. McDonald, could it hold to later? Dr. Harry, is it necessary to proceed now with your question? Dr. Rhomberg.

DR. HARRY: No, it can wait.

DR. KENDALL: Excellent. Proceed, Dr. Setzer.

DR. SETZER: When we couldn't get estimates for all the parameters, we proceeded in this order. Of course, first, we fit the full model using sex-specific values for B and random effects for B. Next step, since we'd already observed that it was pretty common for B to be similar between the sexes, to try single value with B with

random use with B.

The next step would have if that, again, didn't converge, try sex-specific values for B but no random effects. And, finally, to try to estimate a single value with B with no random effects. And then if all those failed, we'd use an approach I'm going to describe in a minute to identify sex-specific value of B that were consistent with the data and then estimate the other parameters given those sex-specific values.

I'll say that, in this estimation process, we only basically only approaches one, two -- they're not numbered here. But the first one, the second one, and the last one actually ended up being used. If we couldn't get estimates even for a single value of B with random effects, none of the other approaches worked either.

So in those cases where we can't estimate a value of P sub B, and it's just under half of the chemicals where this happens, how do we do it? The basic approach is to use the fact that we can calculate a likelihood for the model on the given data and identify values of P sub B that are consistent with the data by trying different values of P sub B, estimating the other parameters, and calculating the likelihood of the result, and then finding that value of P that is on the maximum of that surface or at least is consistent with the maximum of the surface in cases where the surface is very flat.

Just in review, the log likelihood is a measure of the degree to which the data supported a particular parameter. This approach I'm describing is generally called is "Profile Likelihood." It's most commonly for calculating confidence levels for a parameter. And the rest of that slide just goes what I already said.

In detail, we set this parameter P sub B. Remember, there is a separate value for males and females. This is really two parameters. We're fixed in turn to each point on an 11 by 11 grid ranging from .001 to .999.

At each point for each of those values of P sub B for males and females, we fixed the value to an point and then estimate the rest of the remaining parameters, calculate the log likelihood, and plot it on a grid. And to aid visualization, values were linearly interpolated between grid points. We selected the grid point with the largest log likelihood as the value of P sub B that we used for the estimate of the other parameters.

Here's a graph of one of those plots. In this particular case, the highest value is down here in the lower corner. We can see that as we progress from bright yellow to -- yellow, my wife corrects me -- as we go from the bright yellowed to red, the surface is dropping off. I'm using the intervals here are based on minus 2 times the difference of

log likelihood between the maximum value and the interpolated points here. So these sort of roughly corresponds to confidence intervals, confidence contours for the parameter if we were estimating it. Red would then correspond to values that are significant at .95, or .05, whichever way you count it.

Furthermore, we identified grid points that aren't -- not only aren't significantly different from the maximum value by open circles, the remainders are pluses indicate that they are significant.

Missing points indicate models that for some reason didn't converge. So there are a few up in there here, and there are a bunch out here.

One thing we can get at is to what extent -- what is important to know is since we're not jointly estimating our parameters with the horizontal asymptote parameters with the other parameters, it's important to know something about the sensitivity. How much would our estimate of benchmark dose change if we picked a different value.

So basically on the same kind of grid we plotted the profile likelihood plot, plot benchmark dose then this is fraction of the value at the selected point. And this is something that is not in the December draft, but was something I've done since December.

So we plot contours, again, plot contours like we did the

likelihood plots. And in the figure I'm about to show you, the smallest, contour that's closest to the estimate, corresponds to a plus or mine 25 percent in change in benchmark dose.

Okay. And again this is the same chemical we saw before or we saw the profile likelihood before, and we can see that, basically, we -- well, within 25 percent, the same estimate of benchmark dose regardless of what value we chose. For the male benchmark dose, over a wide range of estimates of B, we don't get a change.

I want to move on to the expanded model that Dr. Portier was talking about. Some of the data sets looked like there was a low dose shoulder. And the approached we used in the July draft, there generally weren't enough doses to actually examine that. One of the advantages of aggregating the data sets is that it allows to us build a somewhat more complicated model to look at that.

One of the explanations for this low-dose shoulder is existence of saturable metabolic clearance of the parent compound. The approach I used here is a little bit different from sort of a standard statistical approach, was to build a submodel which was inspired by this mechanism -- and I want to emphasize the word inspired -- to the basic model which would create that low-dose shoulder. And the point part was to keep the model simple. We don't have the data to

parameterize a real biologically based dose response model for these chemicals. Nevertheless, we have some information to allow us to use some biological ideas to develop a model shape.

The approach is to build a very simple PBPK model. This is useful conceptually, not for the parameterization but to get a sense of the shape of the submodel we're going to use. This model has two compartments, a liver and everything else. We're sending oral dosing. One hundred percent of the oral dose goes into the portal circulations so it goes into the liver for metabolism.

And then there are venous and arterial circulation. And we only considered saturable metabolic clearance of the parent compound and first order of renal clearance.

It turns out when you write down the differential equations for this model, they are simple enough you can solve explicitly for steady state.

Now, you can write down now then, if you assume dose is the administered dose rate, and you describe the concentration in the rest of the body part of that compartment of that model as I dose or internal dose, this is the steady state. It's in constant dosing. And you get these two parameters, S and D, which are these functions of the pharmacokinetic parameters.

In principle, if we had the information and particularly what we don't have are metabolic information -- sorry -- metabolism information and measure of renal clearance, we could have used the biological parameters to parameterize this.

Instead we treat this model as an empirical model and estimate S and D as empirical parameters just like the others. So the way we use this model then is to compose the two models. We have the internal dose model, which describes internal dose in terms as a function of administered dose. And then we use the basic model, the exponential model we've been talking about, that describes the relationship between internal dose and the response, the cholinesterase activity.

To show you what this looks like.

The dotted lines show the shape of this internal dose model for different values of S and for one value of D. The names come if D from displacement because it acts like a displacement of this internal dose model. S describes the shape. Where S is very small you get a very dog-legged like shape, as S gets larger you get a more smooth shape.

All of these curves will eventually converge to a shape that's parallel to the internal dose equals external dose line. One thing that S does is control the rate of convergence of that actual model to that

parallel line.

If you combine this model with the basic model, you get dose response shapes that look like this. And this what we actually see when you compare the data. Again, when S is very small, you get an almost threshold-like model, although this isn't really a threshold. It's a smooth curve.

As S gets larger, you have a more smoother curve. And finally, as S gets relatively large -- as we talked about before, as S gets large without bound, you can converge to the basic model.

That's also true as D gets small, as you can see, if you slide this dotted line back towards the origin you get closer -- as D is zero you, in fact, do get the basic model. The rate of convergence depends on the actual value of S that's happening.

It's currently difficult to estimate parameters in this model using the NLME function. And I don't understand why and that's something working on right now. But we can still estimate values of S and D fairly well by, again, using the reasonable profile likelihood approach that we described for P sub B.

The main consequence of doing things this way is that it makes it somewhat more difficult to get reliable estimates of the confidence levels for the benchmark dose since they don't take into account

estimating S and D in the process. And that's why I want to keep working on doing it the other way.

I have to fess up here. Due to some programming errors in the analysis before the December draft, we were only able to calculate the profile likelihood plot for a small number of chemicals; and those were wrong. And the main consequence of the programming errors was -- actually, the subsequent analysis where we actually then estimate D, for example, for the chemicals, those, I believe, were correct. So the main consequence of this was to limit the number of chemicals which benchmark doses could be calculated using the expand model.

Right now we've got profile likelihood for all 29 chemicals. And 17 of those 29 chemicals, the fit for the expanded model is significantly improved over the basic model. And there's a list of the chemicals for which that's true.

Here's an example profile likelihood estimate surface for S and D for bensulide. The scale is the same. So these are probability steps going down. The actual scales for S and D depend on the dose scale used. So if the largest dose in the study is very small, these will range over a small range; if these are very large, these will range over a much larger range.

And some dose response plots. I'm afraid these don't show up

very well I have to learn to use wider lines when I make these graphs. These were a little bit busy and hard to see. So let's go through some of them.

The individual points are individual dose means from individual data sets. So this is essentially every individual dose mean in all the data sets plotted versus dose. For the same in this case in bensulide, there was only one set of units used so all the data are on one graph.

The solid lines are the dose responses that correspond to the population mean parameters values for all the parameters. The colors indicate values for males and for females; blue indicates male; red indicates females. The dotted lines indicate mean values for each individual study.

So in this case, it looks like there were two studies, to two separate studies, for bensulide with somewhat different background levels so you get these separated values.

And then what you don't see on this graph is with each individual study may have multiple data sets. You can sort of see the values, the doses sort of piling up here at discrete dose levels. And when we look at residuals in a minute, you'll see that.

This is the basic model. You can see that it's an exponential model. It just drops. For the expanded model, you see the shoulder

that, adding the expanded model, the internal dose model adds to the dose response curve.

Residual plots on the left side are the residuals are the basic model; on the right side are residuals from the expanded model. What you see here is an excess of positive residuals down around 10 percent. What we're plotting here is the residuals from the model fit. That is the difference between the actual observed mean and the model-predicted mean for each individual data set -- this is the particular mean for each individual data set -- scaled by its predicted standard error, plotted against the fraction of inhibition predicted by the model.

We see that in the basic model at around 10 percent, which is where we want to put our benchmark dose, we are overestimating the degree of inhibition. And that's consistent with the graphs I showed you before with the shoulder.

If we move to the model with low dose curvature with the expanded model, we see that the residuals are more uniformly or more evenly scattered around this horizontal line that indicates zero. So basically what that means is we're over-predicting about as often as we're under-predicting, which is sort of when we're looking.

This is just a slide of the table of the chemicals and the relative

potency factors, I think, from the December draft of the document and points of departure.

Summary. In summary, we attempted to address SAP recommendations; and we believe we've improved benchmark-dose calculations. We've used profile likelihood to estimate the horizontal asymptotes results which gives us a value that's consistent with the data. That's superior to sort of assuming that it's zero.

By switching to benchmark dose, our measure of -- is our basis for calculating relative potency. We have a measure that's less sensitive to our estimated horizontal asymptote than was the slope factor that we were using before. And by changing the weight function, we've improved somewhat the quality of the estimate we've done.

We've reparameterized the basic model to improve the stability of the estimator. This allows -- essentially what that means is we have convergence more often and it's easier to get convergence when you do get it.

By estimating parameters for combined data sets, we can introduce a slightly more complicated model that describes the low-dose shoulder of the dose response. And that, in fact, does give us -- it improves the fit to the data and improves the benchmark dose

estimate at least for quite a number of chemicals.

And that so should be all. Yes, that's it.

DR. KENDALL: Thank you very much for that informative presentation. Any quick questions from the Panel? Otherwise -- okay. Dr. Durkin.

DR. DURKIN: Woody, very, very quick. I'm a little dense.

DR. SETZER: No, you're not.

DR. DURKIN: You did, prior to combining studies, everything was scaled -- correct? -- scaled for the differences in the background risk response rates among the studies the way you reparametarized it.

DR. SETZER: Well, actually, yes or no. The parameterization of the model sort of does that by estimating -- we have not explicitly scaled it in the sense of going through and dividing by the background for that particular data set.

What we do have is a multiplier for the model for each data set that sort of takes that into account. That's what the random of both the --

DR. DURKIN: That's one of the random --

DR. SETZER: Well, there's actually a fixed effect because we -- there's a fixed effect that affects sex and units, and there's a random effect term that affects data sets and studies; yeah.

DR. DURKIN: That explains that figure for me. Thanks.

DR. SETZER: Thanks.

DR. KENDALL: Dr. Roberts.

DR. ROBERTS: Just a quick question. Are you proposing to go forward with the benchmark doses based on the expanded model for all of the chemicals or for some of them with the expanded model and some of them with the basic model?

DR. SETZER: Certainly -- this is probably a policy decision that I'm not really supposed to make. But I would think that, certainly, in those cases where the expanded model describes the data substantially better than did the basic model, that's where the benchmark dose would come from.

The question -- the only issues would be in situations where there's not really a lot of evidence to support the expanded mode over the basic model for a given data set.

DR. ROBERTS: Is there any down side from a technical standpoint just using the expanded model for the complete data set for all of the OPs?

DR. SETZER: I'm trying to balance, sort of model uncertainty parameters versus uncertainty in parameter estimation in this. But, basically, what happens is as you estimate more parameters in a model

like this, you sort of increase the confidence intervals on the parameters you've estimated. You generally want to use simpler models if you can.

On the other hand, you can introduce some bias by not having the right model. And so that's the tradeoff you're trying to balance.

DR. KENDALL: For the Panel, I have four or five people that want to ask questions. If I do so, it will take another half an hour. I would propose, if there's something quick that Dr. Setzer needs to address, let's do that versus let's get into the depth of discussion that I think you really want to engage when we have a chance to reconvene.

So if there is any clarification -- Dr. Rhomberg, your hand was up. Is there a clarification from you needed?

DR. RHOMBERG: it's a clarification.

DR. KENDALL: Then let's do that.

DR. RHOMBERG: I'll state it. And if we want to defer it, I will defer the answer.

DR. KENDALL: Okay. Go ahead.

DR. RHOMBERG: What my question is about S and D in the expanded model. In the December document, not only did you have to use profile likelihood a lot of the time, but you even had difficulty with that in that you had a hard time in finding a spot on the surface

where there was really clear differentiation. And I think you solved that by setting S very small and then estimating D.

You didn't mention that problem now. Has that gone away with the fixes you made to the calculations?

DR. SETZER: I wish. No, but what I'm trying to do now is trying to understand better why I'm having that trouble. What I would do, if we can't get -- I mean, it has not gone away. That's probably the easiest way to answer that right now. And if you want more, we can talk more about it.

DR. KENDALL: Dr. Conolly.

DR. CONOLLY: I'll keep it brief, also.

DR. KENDALL: Please.

DR. CONOLLY: Woody, the expanded model, you said, I think, was motivated by knowledge that OP clearances are determined by saturable processes, carboxyesterases (ph), and things like that. And the question I've got for you -- and we can go into that in more depth later if it's a long answer -- is just whether you feel the validity or enthusiasm of using the expanded model in the assessment is really dependant on that interpretation because I might challenge you that biological interpretation of the model, not necessarily on the application of the model.

DR. SETZER: That's fine. And I would -- no, it's not dependant on that. In fact, I tried to emphasize that. But that's for asking because I get to say it again.

No, that's why I used the word "inspired" by that idea. Basically, what we're looking for, what seemed seems to characterize the belief or the information that we have is that we expect there to be some sort -- it's -- I'm going to get myself into a more complicated explanation than I want.

No. It's essentially an empirical model that allows us to modify the dose response shape in a way that focuses on the low-dose end as opposed, for example, adding polynomials or putting a power on dose which would effect the entire dose range.

DR. MCCONNELL: I think calling it an empirical modeling is probably the safest way to go forward.

DR. SETZER: That's right.

DR. KENDALL: Dr. Harry.

DR. HARRY: I'll wait.

DR. KENDALL: Dr. MacDonald.

DR. MACDONALD: Yeah, I've got two questions and I think they have short answers.

One is do you think what you had problems getting the fit to

work that could be the result of combining contradictory data sets?

DR. SETZER: For one chemical, that might be the case. But, generally, no, I don't think so.

DR. MACDONALD: And, also, you raised a very good issue about the confidence intervals getting wider when you start fitting more things. I'm not sure everyone appreciates the importance of that. But it really makes me worry about anything that's going to be based on confidence intervals like BMDL because you can always just make more assumptions your confidence intervals get tighter and everybody feels better.

DR. SETZER: Yeah, that's actually one of the problems; isn't it. Yeah.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I'm not going to let you rush me, Mr. Chairman. I have a lot of questions concerning things that are not in the write-up about the procedures that I want to be sure I understand rather than assuming I understand what they are. Hopefully, it won't take more than about 10 minutes; but I have a number of questions that I have to ask.

DR. KENDALL: Sounds to me that that might be best engaged when we reconvene, Chris.

DR. PORTIER: It's up to you. These are all clarification issues. They are not any further discussion of the other issues. This is one of my concerns was that we would rush through this very important aspect of this presentation. A lot of what's done is going to be dependent on this. So if we're going rush to get my comments in now, yes, I would prefer to put them off. But if not, I would prefer to do them now since the topic is fresh in everyone's mind. I will let you decide that.

DR. RHOMBERG: Comments?

DR. KENDALL: Dr. Rhomberg.

DR. RHOMBERG: Once we get to that point, I'm sure I will have a lot of comments and questions as well that are also, at least on the cusp between things that are clarifications and that are discussions. If you start asking yours, I'm probably going to feel like asking mine.

DR. KENDALL: See, that's what I'm worried about. My druthers were to cut it off completely after the presentation by Woody, but I didn't. I think we did a good job to trying to get a few of these issues on the table. But I appreciate your honesty. If you've got multiple ones, what I'm afraid is you will get into it, others are going to get into it. We're substantially ahead of schedule now.

DR. RHOMBERG: I don't just want to agree that I don't want to rush the issue, and I think that saying we don't want to rush the issue is a very important point that Chris made.

DR. KENDALL: And because of that, I'd say it's very difficult -- and one of the things I've found it is very difficult for people to get out and get back in an hour. If I had a few more minutes -- I'm going to reconvene precisely at 1:30. Okay. In that way, you got a few more minutes than an hour to get back here because I'm going to start at 1:30. Dr. Portier, will you bear with me?

DR. PORTIER: I'd be happy to. That's great.

DR. KENDALL: We will close this morning session and reconvene at 1:30 p.m. Thank you.

[Lunch recess was taken.]

DR. KENDALL: This will reconvene the FIFRA Advisory Panel. We concluded with an very excellent presentation by EPA in our morning session. And now we have the questions for the SAP on Hazards and Relative Potency Factors. I would like to have those questions posed.

I know there are some clarifications, additional discussion, related to your presentation. Let's go ahead and present the questions, and then we'll proceed forward with the clarification, then move into

the questions. Thank you.

Go ahead. And let's present the first question. Just the first one only.

DR. LOWIT: In September 2001, the FIFRA SAP made some specific recommendations to the Agency concerning refinements of its dose response analysis of cholinesterase on organophosphates. Some of these include the deviation of the adjustment factors "B" and the modification for use of "B"; a formal analysis of the residues; minor revision to the Agency OP-CRA Assessment Program including the revision of calculations of the goodness of fit statistic and deletion on the p- and t-values PND; consideration of the appropriate measures of relative potency; expression of the inhalation exposure in the same units as the oral doses and adjustment for actual treatment durations; consideration of the impact of individual animal data instead of summary information; and derivation of oral doses from the all dietary intake rates.

Part B of the same question. You are asked to comment on how to address the recommendations.

DR. KENDALL: Okay.

DR. LOWIT: Part B of the same question. Several of these issues were addressed by the application of the nonlinear mixed effect

for combining cholinesterase data. In addition, EPA utilized the profile likelihood method for estimating horizontal asymptotes when they could not be estimated jointly with the other parameters. And we're, also, asking you to comment on the use of these statistical procedures and the dose responses.

DR. KENDALL: Okay. Thank you very much. As we concluded the morning session, Dr. Portier, you had two questions that you wanted some time to address. Dr. Rhomberg, also, has some points. Why don't you proceed.

DR. PORTIER: I didn't say two. I said 10 minutes of questions.

DR. KENDALL: Two questions for 10 minutes or 10 minutes for two questions?

DR. PORTIER: I think it's 10 questions for one minute each. Just, again, these are all clarifications questions, I hope.

In page five of the write up, you basically describe what you did last time. And in page 9, you describe what you're doing now in terms of full data sets versus data sets. You didn't come in on the dilution of doses issue. Is there no dilution of dose groups in the current analysis?

DR. SETZER: That's correct.

DR. PORTIER: In the previous version you had average parameter values for each study and then average values for each OP across studies and each time across studies and everything like that. I just want to be clear that I'm understanding what you're doing now. When you analyzed all the data, it is literally for an OP all the data sets; is that correct?

DR. SETZER: That's correct.

DR. PORTIER: And then there's one potency factor that comes off for an OP from that calculation;

DR. SETZER: That's correct.

DR. PORTIER: Which is the grand mean in some sense.

DR. SETZER: In some sense, yes.

DR. PORTIER: You discussed steady state in loss terms in this overall analysis. And I didn't see anything in here -- and correct me if it is in here -- describing half-lifes in male rats, female rats.

DR. SETZER: No.

DR. PORTIER: Or humans. Half lives of the OPs in the animals or in the humans to discuss, to verify, your assumption about a 21-day steady state value.

DR. SETZER: The steady state value we're talking about doesn't refer -- it refers to cholinesterase activity not to whatever

tissue-specific levels of the OP. So it's an empirically determined value. Actually, it's the same thing we talked about in the September meeting, the cholinesterase, the inhibition stabilize around 21 days.

DR. PORTIER: But there's no formal analysis anywhere in here that verifies that statement about the steady state nature of cholinesterase inhibition under constant exposure for 21 days.

DR. SETZER: Other than the analysis we presented in September, there's no new analysis.

DR. PORTIER: On page 7, let me go back to my notes here. Oh, yes. On page 7, the top of the page in terms of points of departure, you say the BMD10 was selected at the effect level for point of departure because this level is generally at or near the limit of sensitivity for discerning the statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

My question was: Were there any evaluations done of other BMDs instead of 10 percent, 5 percent, 1 percent to compare against this?

DR. SETZER: No.

DR. PORTIER: And you discuss about them being close to the limit of statistical significance. Did you take any view of looking at

the co-efficient of variations in the sense of the BMD10 in variances and looking at what that looks like.

DR. SETZER: You mean looking at how the confidence level would change as we change the response level? No, we haven't.

DR. PORTIER: Okay. I assume, and maybe I'm assuming wrong, that all of the error distributions in the model are normal.

DR. SETZER: They're assumed to be normal; that's correct.

DR. PORTIER: Was any sensitivity analysis done for this?

DR. SETZER: No.

DR. PORTIER: I'm assuming no log transformation was made on the Y-response variable to see the cholinesterase levels?

DR. SETZER: That's correct. The data we modeled were on the original scale.

DR. PORTIER: I'll make a comment. This is sort of an off-the-cuff comment. But if any revised version, I would have preferred to have seen a standard statistical presentation of the expected value of Y is or a Y is this plus error structure and then break out of the error structure for me so I could understand the nesting of the error structure better. That would have been very useful.

Again, I want to verify that in the likelihood-based procedure

you are using, you are actually using a normal likelihood and not the sum of squared errors.

DR. SETZER: In the particular procedure we're using, which is has been called conditional linearized, it's an approximate log likelihood -- it's an approximation based on some linearizations based on a normal likelihood, yes. On a normal likelihood approach for all.

DR. PORTIER: The error terms. The error terms are proffering into --

DR. SETZER: That's correct.

DR. PORTIER: -- into the normal distribution.

In looking at your starting points or calculation what you called the profile likelihood, I assume that for each point in the grid you have shown me that surface that you were showing me that maximization was done for all the other parameters under at fixed B value.

DR. SETZER: That's correct. With this caveat. Optimization was done. Remember this is a -- this is not an exact maximum likelihood procedure because it's based on a linearized likelihood. But, yes, for all the other parameters were estimated using the procedure conditional on the value of the fixed value from the P sub B, or the S and Ds, depending on the ones you're talking about.

DR. PORTIER: Okay. In looking at the actual format of the

model under varying studies, varying sex, varying species, varying times of observation, I was a little lost as to how these effects were entered into there. I'll tell what I assume the effects, how they were entered into there. For each study you had a variable for background adjustment to the grand mean of background and each of those variables had their own distribution from which they were derived. Was it a mean structure cross? What exactly are you doing with that one.

DR. SETZER: Okay. You have the basic model in terms -- if you're talking about the basic model. We have a parameter that indicates that qualifies the background. We had horizontal asymptotes in the benchmark dose. We fit a model in which there's a separate grand mean, fixed grand mean, for the background values for the cross of sex and unit in which cholinesterase is measure because we studies where different units were used. And the units indicate different methodologies. It's just sort of rescaleing the units to the right answer in dealing with the different units.

And then a separate grand mean for sexes for the horizontal asymptotes and benchmark dose. Then the variances model, for each of those three parameters, is a considered the sum of that main effect. And two random variables each with mean zero and their own

variances. One random effect for among study availability and one among data sets that study variability. That's if we're counting, that means six random parameters and six variances to be estimated. We assume to be independent, but there just aren't enough data to estimate covariances among those variables. So it's essentially the co-variances measures is diagonal.

DR. PORTIER: That confused me, then, about one of your plots. I thought I had understood that is what you had done. Then I don't understand how you got the plot -- let's see if I can find the one I'm talking about -- dose response shape at low doses.

DR. SETZER: Yeah.

DR. PORTIER: It was the one that had three plots on it with the grand mean plot. This is from his presentation. A grand mean plot and a plot above and a plot below.

DR. SETZER: It might be 42.

DR. SETZER: It says --

DR. PORTIER: My slides are not in color, so I'm -- it was definitely toward the end. Three or four or five slides back from the summary.

DR. SETZER: There.

DR. PORTIER: This is the one. I'm a little bit confused about

how you get the different backgrounds for the different models if it's a random effect to tie it down for a particular study.

DR. SETZER: For each study and, indeed, for each data set within study, you get kind of a -- well, you can get a maximum model estimate for the mean value for the parameter for that study or data set. What I've shown on these plots, the solid curves correspond to the grand means to the dose response curves corresponds to the grand means. The dashed curves correspond to those response curves for the study specific value which would be the grand mean plus the estimate of the particular random effect for that study and so forth.

And I only did it one level of nesting down because it would get too confusing to do it...

DR. PORTIER: Okay. That's good. I understand that now. Again, I didn't get into the code of R and sit down and look at it, I just wanted make sure that the NMLE methodology cannot do constrained parameter estimation.

DR. SETZER: That's correct.

DR. PORTIER: Which is why you did all the log transforms.

DR. SETZER: That's correct.

DR. PORTIER: Page 19, you describe the likelihood ration test. It's at the bottom of the page, significance of the fit based upon

the additional bigger model. Do you see where I am?

DR. SETZER: Yeah. I see where you are.

DR. PORTIER: I'm curious about the degrees of freedom for this likelihood ratio test. What were you using?

DR. SETZER: Two.

DR. PORTIER: Two. Even so though the model sort of collapses, when you send either one of the parameters to its boundary value, it brings you back to the basic model.

DR. SETZER: That's a good point.

DR. PORTIER: You're still using two.

DR. SETZER: I'm still using two.

DR. PORTIER: That's probably not bad or good. I'm trying to make sure I clearly understand everything.

Finally, the steady state solution off of the PBPK model that you're using. I didn't sit down and do it myself, but I need some degree of assurance in looking at this. It didn't appear to me that that type of PPBK model should have had a point of discontinuity in it which, obviously, the steady state solution does have a point of discontinuity in it.

I wanted to make sure there weren't assumptions that I didn't see that went into that model in terms of how it would react or how it

would work. Continuous, the PBPK model itself is a continuous time, continuous dose system of augmenting differential equations. Even in steady state, I don't see how hat would lead to a nonsmooth response. And yet you got this minus S which is clearly a point of discontinuity.

DR. SETZER: Can we go to the next slide?

DR. PORTIER: There your solution for I dose introduces a break point in the dose response curve which I didn't see in the system itself. And since I didn't have the LDs in front of me, I couldn't.

Are you absolutely certain of what you did.

DR. SETZER: Yeah. Never ask me if I'm absolutely certain of everything, Chris. However, I'm reasonably certain that this solves that system. That's the result of actually -- I mean I cheated. I used MAPLE which is no guarantee that it's right. Although given -- nor done by hand.

Actually, in a sense, that may not be that important. We're not trying to claim that this is. In fact that's the wrong pharmacokinetic model in some sense anyway. The point is to use a sort of simple conceptual model to help you derive a mathematical expression to use in a dose response model that would have the characteristics that I wanted which would cause that shoulder at low doses and have that sort of localized at the low rate it occurred; and localize that to a

greater or lesser degree, which I contend this curve does; although, computationally, it may be a bit of a problem.

Singularly, I'm talking about S and D, if you're going to drop at all, they have to be positive in that model.

DR. PORTIER: I agree.

DR. SETZER: So where's the point of discontinuity that you're talking about?

DR. PORTIER: My concern is for dose less than

DR. SETZER: I see what you mean. But there's a trick there in that positive square root. It turns out that when dose is less than S, the thing under the positive square root of that under that radical cancels it out. So if dose less than S or less than D essentially, you get a flat line, horizontal line.

DR. PORTIER: That's my point. That implies that for dose less than S --

DR. SETZER: You can get perfect metabolism much in the first pass.

DR. PORTIER: Exactly, that the steady state solution is a zero steady state.

DR. SETZER: That's a good point.

DR. PORTIER: Which in the early DEEMS I find difficult to

understand. That's all. I hope it wasn't more than 10 minutes.

DR. KENDALL: Very well. Aren't you glad we waited, Dr. Portier?

DR. PORTIER: I'm glad. Dr. Rhomberg.

DR. RHOMBERG: The reason I was raising my hand earlier was I was wondering if this last question didn't actually have something to do with the question I asked just before the break about the actual estimation of values for S and D If you choose a really small value for S, I think it is, and then putting it at the edge of your space of values that you've tried and then optimized D, I think that makes for a very sharp effect so that the curve are actually curves. I don't know if Chris was reacting to the equation here for the singularity or for the actual pictures of the curves.

For my part, the same question arose, but it was looking at the curves that actually seem to be dead flat and then there seems to be actually a little break there and start to go down. I ascribe to the fact that by making S very small and D very large, you were basically making some very sharp kind of rectangular -- although it's continuous on a microscale. It looks like it's a break on the scale that you were plotting out.

Is that a reasonable explanation of that effect?

DR. SETZER: The reason and -- in the December draft the motive for fixing S as a particular value was that when we looked at the profile likelihood response dose for chemicals we actually got something out. It actually looked like, for each of those chemicals, the maximum -- the likelihood was actually for a very, very small value of S.

And so what we were doing was essentially analogous of what I've done the estimating P sub Bs. If I can't explain the majority, use the profile likelihood to give me a plausible value for one of the parameters and estimate the other one.

But it's true. That for a very small values of S, I showed that on the graph, too. I talked about this curve. That as S gets small, the curve looks more and more like a sort of a classical threshold model. And to some extent, that was an artifact of some programming error. Those figures were wrong.

DR. RHOMBERG: The figure that you showed this time. And I should remember which slide number it is now. The one that actually shows the curves with the shoulder. And in this case, the one you showed today behaving much rounder and more nicely behaved.

DR. SETZER: Yes, sir.

DR. RHOMBERG: Is that typical of the way they looked or is

that atypical?

DR. SETZER: It's not atypical. There's a variety of shapes from barely discerning a shoulder to all the way to something that looks like the curve we showed before.

DR. RHOMBERG: Okay. I guess Dr. Portier asked a lot of the questions I was going to ask. But there's one part that you started on and didn't quite finish. And that is I guess the way I would rephrase it is choice of starting values for some of these cases where you are now doing profile likelihood.

And I'm not sure I quite follow the explanation in the text about where you got the starting values from for the parameters that you're now reoptmizing when you're doing S and D And in particular, what happens when -- I guess now in this version, you no longer have the case of setting B to zero, but you do have cases where you had to do tricks to estimate B even in the basic model. Where does the starting value for B come from, then, when you're considering the expanded model.

DR. SETZER: Yeah. Well, we start in the expanded model. We start essentially with the basic model that we ended up with. So whatever effects we estimated or probably didn't estimate in the basic model we start there. So if we had to fix B and used profile likelihood

as the basis model to fix it, the I kept B fixed at that value. If B was estimated in the previous model, it continues to be estimated and so forth. If it's estimated that B varies B's allowed to vary. If B was fixed, at this point there's no effort to sort of reinsert essentially do a three-dimensional profile likelihood or four-dimensional profile likelihood to determine the sort of the best combination of S, D, and P sub B for that.

DR. RHOMBERG: I guess you could be forgiven for that. I guess what I was wondering the degree to which -- these things can draft such that B that you get. So to the degree that B interacts with S and D, could it be that when you add S and D into the equation, you no longer have the problem that B needs to be fixed the way it had to before with the basic model; or has that situation not arise?

DR. SETZER: Basically, that's possible. But I don't think that's going to happen.

DR. RHOMBERG: All right.

DR. SETZER: Because of some efforts I made at trying, I thought of that and tried to sort of refit things but unsuccessfully so far.

DR. RHOMBERG: I have one other clarification question and that is on the different units. I'll confess to not knowing exactly how

they assays run. I understand why you did them differently. These are not things you can convert back and forth because they are actually different methodologies that might be measuring somewhat difference things and not just measuring units. That's what you were saying earlier; right?

DR. SETZER: That's correct.

DR. RHOMBERG: Can you at least say that these measures ought to be sort of linearly related to one another? I guess the one I'm worried about is the Delta pH which since pH is on a log scale, in a sense implicitly log transforming results for one thing and that's not being done for some of the other things. Does that cause any issue?

DR. SETZER: That's a good point about log Delta's pH. There are, in fact, some published conversions between pH method for cholinesterase activity and one of the other methods. They turn out to be linear transformations nonzero intercept. One of the approaches, I think for rats, that intercept is quite small. It's not sufficient you have a linear transformation for that to work. I think it needs to be a pure scale transformation.

The intercept, at least, I think for rats for one of that is the intercept is quite small relative to the magnitude is the a product of the slope. It's approximately right.

DR. RHOMBERG: So it's not a practical issue, you don't think.

DR. SETZER: I don't think it's a practical issue.

DR. RHOMBERG: Thank you.

DR. KENDALL: Thank Dr. Rhomberg. Any others want some clarification? Dr. Harry.

DR. HARRY: Of the last question where you were talking about the different types. And what I was concerned about, and I saw how you were handling the different types of assays to bring them back to some sort of comparison. But while you think about the data, did you take into consideration why you had a prescreen to say good studies that you wanted to look at, was there a component point that took into consideration the differential sensitivity of these different assays?

We have different ways of looking at things. Have different assays been looked at different to say their levels of sensitivity. I'm concerned about that -- getting down to the really low dose. In some of these assays, they may not, in and of themselves, have the sensitivity to pick up accurately small changes. So you might be missing something. Was there any way of weighing that or anything?

DR. SETZER: I'm wondering if you're not asking the question that was asked a littler earlier but in a different way.

If the differential sensitivity is you expect there to be a bias at the low-dose end and a mean value to get it out. Or is it that you expect the variances to grow as you get down to low-dose ends so that there is just a lot of noise down there and you can't -- if you're doing calibration for NOAELs or something, you don't have a lot of sensitivity to see significant differences.

If it's the latter situation, I think the weighting we've done sort of accounts for that. Basically, the data sets were larger variances will contribute less to the overall mean estimate. If it's the former where there's a bias, a real bias, it gets more pronounced as inhibition gets smaller.

I certainly haven't adjusted for that mathematically. Whether in the screening process for studies, that was taken into account. I'd have to get somebody else to answer.

DR. HARRY: This particular question is more on the bias. On the first component of it on maybe the bias rather than the variability. Because if you are outside or below the ability of an assay to truly detect change because of the sensitivity of the assay, and that may also come into play as you're getting new technology to pick it up. So we have a lot of data across a large sensitive assay to pick it up. So it's not so much the variability, but you may see no changes detectable

coming in you're going to have to deal with that. I was just wondering if anyone had taken that into consideration.

DR. SETZER: I haven't mathematically.

DR. BRIMIJOIN: We're talking about the low end of an inhibition curve not the low end of a activity curve. So where an assay would be perfectly good in this zone.

DR. HARRY: But it may be misleading.

DR. BRIMIJOIN: So it really does come back to the question not of sensitivity of the assay but precision.

DR. SETZER: Correct.

DR. BRIMIJOIN: It's folded into the measure the variances.

DR. SETZER: Thank you.

DR. KENDALL: Any further comments to that question or issue? Dr. Portier.

Did you want to say anything Dr. Lowit? Did you want to say anything to this? Okay. I think we got that at least resolved.

Next clarification issue, Dr. Portier.

DR. PORTIER: Yeah. I'd forgotten to pick that one from my list, but I remember what it is. We didn't hear any discussion or presentation on the CELs for the acute tox studies and the comparison of them against benchmark doses. And there's some points in there

about these models couldn't be fit to those data. Will we get a presentation on that?

DR. LOWIT: We're going to hold the discussion on the different time frames and all the hazard conditions that come along with that until Friday when we discuss with you the last question which is scheduled for Friday in terms of the appropriate time frame for exposure and all the hazard and exposure issues that go into that.

DR. PORTIER: But I'm more interested in questions pertaining to why the dose response analysis was not done with those data is more my question along these lines. There were some statements made that you could not fit model to those data. Yet when I look at that those, data I see five or six dose points. And I'm curious about whether we will get a presentation on that. Or my comments on this first question, I think I should comment on that.

DR. LOWIT: At present time, the acute data in the table that I think you're referring to has not been through any dose response analysis. Those are NOAELs and LOAELs pulled directly out of study reports of data evaluation records and staff toxicology not from the actual study reports themselves.

DR. KENDALL: Any further points?

DR. PERFETTI: Dr. Portier, one thing was referring to

inhalation and the dermal study, a lot of times you may have had more than one dose, several doses; but you only have one time point which, if you model some of those like we did using the original model, you get very, very wide confidence limits. So I mean you're talking about BMDs in the same compartment range from .02 to .12. So it's -- I mean you could do it, but I'm not sure it would be any more accurate than just the CELs.

DR. PORTIER: If I might respond. My comments will reflect when we go to 1A the fact that those large confidences bounds or my lack of confidence in a estimate of BMD10 should in fact reflect on our lack of confidence NOAEL, LOAEL, or any type of dose response assessment from those type data. And it's an indication of a lack of consistent information more than it is an indication of the failure on the regression procedure to give you a descent answer.

DR. KENDALL: Dr. Heeringa.

DR. HEERINGA: A question, Dr. Seltzer.

In your presentation this morning you commented that in several cases that you felt that you may actually be working with a data series. I looked at some of the fits within the model. I don't know whether that's changed in a result of your reanalysis. But it really looked to like you had two different profiles going. It's not just so much a

random effect.

Did you look at this? Did you ever exclude any data series as potentially outliers or poor calibrated or to accept all this, incorporate all the available studies, and treat differences as just the time and effects of population average value?

DR. SETZER: Yes, that's what did. I haven't tried excluding.

DR. HEERINGA: No revisiting. I just looked at the Pomnet (ph) and really in my mind draws two different curves not a random batch.

DR. SETZER: That might be a reasonable thing to do, yes.

DR. KENDALL: Okay. This will close our clarification discussion subsequent to Dr. Setzer's presentation. And now proceeding, the question has been proposed, at least, 1A and B. And proceeding that question I will open it to public comments. If there are any public comments at this time? Are there any public comments?

We have one listed, a Ken Pastoor.

DR. PASTOOR: Good afternoon. My name is Tim Pastoor. I'm with Syngenta Crop Protection and also participate in the IWG.

A couple of comments that we would like to make I think are pertinent in light of both what EPA has already done and I think the information that you're going to be grappling with in the couple of

days to come here.

First of all, I think what we want to do is make sure you understand very clearly that what was done here is a tremendous amount of effort with a very difficult problem. And I think the EPA, Anna Lowit, and Woody Setzer need to be congratulated for the effort that they put into this. It's a tremendous amount of work that was done. I think it's done in a substantial a scientifically credible fashion.

The best way to go about the risk assessment is obviously pick the best endpoint. Use that endpoint that best represents risk characterization. And I think in this kind of situation, they've done a marvelous job of coming up with the proper endpoint, which is female rat brain, representing the dose response characterization, and I think probably the best methodology that you can get, recognizing at the same time that our interpretations of these kinds of data are going to evolve with time. And as we look at these issues as we go forward, there may be different kinds of interpretations. But the work that was done here was probably as well done as you could expect to be done.

One issue we would like to bring up and make sure that the Panel is well aware of the upcoming issues around this is that the BMD10 that was used to establish the relative potency factors was very well done. But it brings into question in the course of the week

when you're looking at the time frames of expression for the risk characterization, the time frames have to match up.

In other words, the BMD10 that we have listed here is based on 21-, 28-day studies, intermediate or chronic studies as some people refer to them. However, when you look at the dietary or residential exposure scenarios, they tend to be short-term exposures if not acute. One day there's a concatenation of acute exposures. So even though we're not we're not dealing with this right now, what we do want to do is apprize you and make sure you understand that will be an issue that I think needs to be very carefully considered by the Panel. Because when you come to the risk characterization process, it would be a numerator and did denominator that have to represent the same time frame for the risk characterization.

So we are very pleased with the effort that the EPA has put into this. The individuals that have been involved in this have done an remarkable job. But we want to make sure that you understand that there is still some things that need to be carefully considered as well.

DR. KENDALL: Thank you, Dr. Pastoor. Any questions form the Panel for him? Thank you very much, sir.

Any further public comments? Okay. Then we'll move into the questions which have been posed. The first one, please comment on

how the Agency addressed the recommendations listed above. We've structured responsibility within the panel, and all of us will contribute. Dr. Brimijoin, would you lead off, please?

DR. BRIMIJOIN: Well, I'm just going to try to moderate this discussion. So we're dealing with Question 1A, which they have divide into seven separate subtopics. And I guess our primary responsibility is to address each of these subtopics and perhaps anything else relevant of this general issue.

DR. KENDALL: The main thing is -

DR. BRIMIJOIN: THE main thing is get the answers to the question.

DR. KENDALL: I think the Agency would desire our feedback on the recommendations we gave them previously.

DR. BRIMIJOIN: Right. So now I have not prepared a point-by-point response to this. In fact, what I would like to do is be the official designated discussion on this Question 1A, myself, Patrick Durkin, Rory Conolly and Eugene McConnell.

The first point the EPA would like to know is our response to its requirements in the dose response analysis, in particular, regarding the derivation of the adjustment Factor B and modification of the decision tree for use in B.

And as I understand it, we are talking about the combined total approaching the final equilibrium level of inhibition at high dose scenario. And this was something which, at the time of the September meeting which I did not participate in, evidently, there were a number of sort of ad hoc solutions in place to deal with this issue.

But the document that we've received and the testimony we've had today from EPA, suggests that this is now been folded into this more sophisticated exponential and expanded exponential data.

So I would like to invite any of my panel members here who would care to comment further on that. Dr. Conolly, for example.

DR. CONOLLY: I don't think I have a lot to add beyond comments that were made this morning about the expanded model. From a biological perspective it makes sense, I think, to have a model that has a shoulder-like behavior. And since I was originally a biologist before I was a modeler, I am happy to see things like that. I'll stop at this point.

DR. BRIMIJOIN: Dr. McConnell. Dr. Durkin.

DR. DURKIN: All of my comments, other than just to commend the Agency for much of what hey have done. I think they're responded to us extremely well. Only on one of the seven issues, and that is the use of individual animal data. And I don't know whether you want to

do that now or just save it.

DR. BRIMIJOIN: Actually, let's reserve that for just a moment. But, in fact, maybe we may be able collapse this discussion, at least among this primary discussants, and always like a comment from anyone else including the other modelers, especially the other modeling people on the SAP.

But so the next question would be as effectively all but the draw of the questions here appear to the appropriateness to adjustments to the model. So, actually, I'd like to know if any of the Panel members are dissatisfied with the treatment of B with the analysis of the residuals. That was a pointed issue in September.

And we've been provided with some graphs that do a person with a sort of typical pharmacologist appreciation for modeling to indicate that it's possible to get fits to these data sets which leave points scattered randomly about the lines as evidence of lack of bias.

We have revisions to the approaches to calculating the goodness of fit statistics. We may want some more discussion on this point of the appropriate measure of relative potency. I think that takes us out of the modeling realm and beginning to impinge on biology and regulation.

So then the first three points, are there any further comments

from anyone on the panel? Dr. Portier.

DR. PORTIER: On all three of these points, I think the EPA has responded as exactly as asked by this Panel from the meeting in September. I commend them on that. I'll note that you might find later I'm not happy with what we asked you to do. That's a whole other issue because seeing it tells you something else. But I want to make you clear that they have addressed exactly what we asked them to address, especially in the handling of the residuals and the change in the test.

DR. BRIMIJOIN: That's how it appeared to me. Let's turn to the appropriate measure of relative potency. I guess, there were two subissues which is the selection of BMD10 as a point of departure and as to whether that does or does not lead to a compromise in the safety factor that's built into the regulatory decision.

And I guess maybe the other subquestion would be about the comparative effects levels when you're dealing with the cases where it's difficult, if not impossible, to calculate a BMD10.

So we already had some discussion of the BMD10 this morning. I think I now understand that this is being used in fact in two ways. And it is being used first as a way of calculating relative potency, but also that selection is likely to drive the estimate of a reference dose

and safety factors.

So, Dr. Conolly, I think you have some insight into these matters.

DR. CONOLLY: Very little. I appreciated the discussion this morning on the two ways to look at the BMD. One to compare relative potency and then the other. And I hadn't considered the other. In fact, I'm looking at it to establish an reference dose.

My own view was if you want to compare the potency of one chemical to another, you picked the best place on the curve to do that. And I know you've given that a lot of thought and you've come up with a BM10, which I guess is okay based on when I heard. But I really can't comment other than that other than you spent a lot more time on this than I have. And if think that is the best way of comparing chemical A to B to C accurately, then I have to go along with you. And that's should be the object. I think the primary objective should be that for the exercise you're trying to do. The other should come much later in your procedures. Is that clear?

DR. SETZER: I think so, yes.

DR. BRIMIJOIN: I think so yes. Pass it down to the fellow.

DR. MCCONNELL: I think the spirit of my comment is much the same of Genes. You know, I think that basically the Agency has

done a good job with a difficult problem. Since as I mentioned earlier, my background is originally in biology and I'm very interested is mechanisms and I spend a lot of time pharmacokinetic mechanisms and pharmacodynamic mechanisms to some extent. And then you realize the complexity of the mechanisms of organophosphate, pharmacokinetics and pharmacodynamics and interactions and so on, you know, to bring out of all of that complexity a workable methodology for assessing cumulative risk is a challenging problem. And you've done this as reasonably as anybody could do it.

I have to say that from sort of a mechanistic biological perspective, I think that what we're doing here is a bit like looking at a basket of fruit that's got, say, an apple, a banana, and then an orange in it and then talking about an average fruit. It's not clear exactly what the means in the real world. But I don't know how to do it better without getting much more complex data sets and much more sophisticated models.

Again, maybe, on the other end of the axis from the -- approach, do it more mechanistically based approach. So it might not sound like it, but this actually is my vote of support for the way relative potency is calculated here.

DR. BRIMIJOIN: Dr. Durkin.

DR. DURKIN: In terms of your approach, other than the comments that I made earlier, I do have a concern that the effect level where you measured the relative potency given the kind of dose response that we have here has to be at the same response level that you would use for your benchmark dose. And you have done that and I have absolutely now quarrel.

If we were reviewing with red blood cell or plasma of cholinesterase, the 10 percent wouldn't even get my attention. That we're applying to brain cholinesterase, it does get my attention. That's not a criticism. I hadn't thought through that prior to coming down the well. And the only thing that I think I would ask for in the document itself is perhaps a little bit more of a biological discussion about if you are going to stick with a 10-percent depression of brain cholinesterase as your point of departure, somewhat of a discussion about what the clinical significance of that might be.

If it was plasma and red blood cells, I think it would almost be trivial. Brain bothers me a little bit more. But in terms of how you used and defined the relative potency, I have absolutely no quarrel.

DR. KENDALL: Dr. Rhomberg.

DR. RHOMBERG: Well, I think you set out the reasons for using the BMD10 very clearly. And I agree with them. I think that the

points were well taken.

I would like to say, though, that I was really sorry to see the reliance on M go away, the shape factor or slope or scale factor, whatever you call it, because that really did reflect the kind of equivalence across compounds that you are relying on for the whole rationale for the whole process. I understand why you had to do that. You had to do that because of the phenomenon of the shoulder. And I suppose, also, for the phenomenon for somewhat confusing calling B here, this. Refers to B in the July document, and that's different from B today which is the logit of PB if am I understanding it correctly.

DR. SETZER: That's right.

DR. RHOMBERG: So I understand why you had to abandon M because it doesn't work any more. But that's very pretty serious that it doesn't work any more. Because that under mines the whole rationale for dose addativity and looking at these things and using any relative potency no matter how well-considered and how well done as a way of adding up doses that are well below the BMD 10 level as ways of getting up towards some degree towards the BMD10 when they're acting together. And I'm not sure what exactly I would do about that.

I think I'm sort of with Rory Conolly here and saying, I don't know how exactly we could do it differently. But I think it's

something that is really of concern and it has to be aired the fact that now that you have dose response curves of different shapes, the very method that you're doing all this comparative potency in order to be able to carry out sort of has a twist on it and it doesn't really hold any more. I think you're sort of and doing it anyway and hoping that it will being close enough.

In view of that and in view of the seriousness of it, I think it would be really be important to try to rescue the notion of a the M factor as a way of looking at relative potency. Perhaps now doing it not in terms of administered dose, but doing it in terms of some kind of internal dose. The trouble is that you have some phenomena that are probably pharmacokinetic and really are not about the mechanism of action of action affecting the shapes of your dose response curves here.

Because you're only -- you're doing everything in terms of administered doses, you have to try to capture those effects in the dose response curve incorrectly and sort of incorrectly ascribing them to things that are really about the mechanism of action this point that you're trying to get descriptions of it as you're trying to capture in those dose response curves.

If you could split those things apart and say you got some

pharmacokinetic things that going on, if we can take care of them separately and then look at once you get some internal dose measures, even if they are empirical and crude, rather than the sophisticated PBPK ones, maybe you can rescue the common shape of the inhibition curve issue which would put you on a much sounder footing and lets you go ahead with the rest of the analysis.

DR. CONOLLY: I would like to say the same to that other than I think discussion needs to start.

DR. RHOMBERG: I would like to underscore Dr. Rhomberg's comments. I share his concerns about dose response analysis for that standpoint although I'm not as optimistic that M can be rescued, at least not in the time frame you have to work with.

On page 1B56 is where you talk about relationships among the dose response curves and acknowledge that they're not going to be parallel for some pretty good biological reasons. And I think that's why we talked about this in previous SAP meetings. Expecting them all to have nice parallel dose response curves is a problem and not realistic given the perhaps the pharmacodynamic and certainly pharmacokinetic.

Also on that section of the document there's sort of a discussion. I was a little bit concerned because the discussion talks

about, sort of deals with this by saying, well, we really think that addativity is probably a reasonable default and assumption for these sort of mixing -- versus the importance of parallelism and dose response curves. I think you're probably right. I haven't seen compelling evidence that there is a significant interaction at which it need to be factored into your risk assessment. So I think you're probably correct in assuming no interaction which would apply addativity.

The question is how you add. And the method selected was the relative toxic potency approach, as Lorenz pointed out, depends upon parallelism and dose response curves depending on where that doesn't exist. So the potency is going to be different depending upon where on the dose response curve you pick to establish that.

And I was one of the folks that sort of argued at the last meeting for BMD10 as opposed to some other -- because it's at the low end of the dose response curve. And it's probably from a practical standpoint about the best that you can do.

But having said that, of course, we're really mostly concerned with exposure that are going to be occurring at one 100th of a BMD10. And that's where the relative potency really matters for the purposes of this cumulative risk assessment. And I don't know that

you have any way to estimate what that BMD.

But I think it needs, as Lorenz says, I think it needs to be dealt with more candidly in the assessment. And this is a potential problem ... fundamental assumption that underlies the approach that we're using in this cumulative risk assessment. And you know, we think that that's a problem for whatever reason or do some kind of analysis that really talks about how this would effect the...

DR. KENDALL: Dr. Portier.

DR. PORTIER: I'm going to different differ with my colleges on this issue. And then I have another point.

First of all, I'm going to reiterate the fact that the Agency has done exactly what we asked them to do. I especially liked the reparameterization to direct the estimate of BMD in the algorithm. I thought that was clever and very useful. But for my comment that's going to come in a minute.

The panel may forget that our discussion regarding the use of potency was the fact that in the previous model the assumption was not dose addativity; the assumption was being used was potency addativity. And under the model that was being used, potency addativity was equivalent to dose addativity.

However, now as Steve has pointed out, we have gone to

models that potential a have different shapes. The Agency has, in fact, stuck with dose addativity by using BMD10. So they have kept to what we asked them to do in terms of clarifying how they're going to deal with the addativity issues... by dose addativity or something else.

So I want to make sure that we don't keep rethrashing through the same argument over and over again. That be clear this time what we want to do with that.

And would have appreciated some discussion of signal-to-noise ratio in the estimates. It's something we raised in our last discussion about how to chose the BMD. Do you choose 10; do you choose 5? And the argument was that you want to choose something that constrains the variance. Optimal variance is probably around 50 for most of these. And so some discussion about how variance relates to mean estimate would have been useful in looking at the BMDs.

I would have, also, have liked some objective demonstration of the choice of the BMD. Not just to use BMD10, but to chose 5, chose 1, chose 10 and then evaluate it and tell me 10 falls within the range 95 percent of the time; 5 falls in the range of the data 65 percent of the time. Just some observations that would allow me to feel more comfortable about the choice of 10 as compared to something else.

Per the question of whether the BMD10 or 5 or whatever that's

chosen for relative potency should be the same one as point of departure, I do agree with that concept in the context of this model; that if we have a optimal choice for a V and R for a response and you chose the BMD for that and do relative potency on that, I'm really happy with that. But what I'm not going to be happy with is that the margin of exposure is always going to be the same if I'm using 10 percent, 5 percent, and 1 percent.

So I think the adjustment is not in terms of what we choose as our point of departure because to me it seems logical to use that as point of departure some optimized ought to be cross multiple data sets that deals with the concept of dose addativity. It's going to be in the margin of exposure that we have to make some adjustments because we're using in this analysis 10 percent and they use some other chemical a few years down the road where they use 1 percent because we have better data. And I think that's where the adjustment factor should be.

DR. BRIMIJOIN: I'm not sure if we can pull. I think we should try and see if we can reach some consensus on this point because EPA wants some specific advise from us. And as you say, they reacted to some specific advise. Before we're now fixating on some fairly obvious problems with that recommendation.

So the question I would pose to my fellow panel members is: Do we go forward saying that BMD10 is a point of departure and elements of relative potency is fraught with problems but is, in fact, the best compromised solution we have at the moment? Do we do as you seem to be suggesting, and it has some attractive features, is ask EPA to reevaluate their data sets. And if they can determine that with without too great a loss in precision, one could go down the scale.

And so we're talking about 5 percent or 2 percent or even 1 percent effects that everyone would be more comfortable with that as a point of departure in lieu of the old days of the no adverse effect level.

So I think we should either, if we can reach any kind of consensus at all, recommend going forward as is with the possibility of reevaluation; or recommending that some sign of internal data or modeling review be conducted and a further decision be reached on the basis of the outcome of that.

We've heard one panel member expressing concern with 10-percent inhibition of brain activity as a possible issue. And, you know, I guess I share that concern even though I'm well aware that it's almost impossible to detect acute effects at a behavioral level or from any inhibition that's much less than about 30 percent, even take 50 percent. And yet I'm, also, uncomfortable with the idea that this

would be kind of the starting point.

-oo0oo-

CERTIFICATE OF STENOTYPE REPORTER

I, Jane F. Hoffman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

_____

JANE F. HOFFMAN

I-N-V-O-I-C-E** ****I-N-V-O-I-C-E****

JANE F. HOFFMAN

849 S. Irving Street

Arlington, VA 22204

SS#305-52-5988

TODAY'S DATE: 2/20/02

DATE TAKEN: 2/05/02

CASE NAME: FIFRA SAP Preliminary Cumulative Risk Assessment

TOTAL: -- PAGES: 262

LOCATION OF DEPO: Arlington, VA

DELIVERY: Regular -- conference rate